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MALARIA

ETIOLOGY, PATHOLOGY, DIAGNOSIS, PROPHYLAXIS, AND TREATMENT

BY

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WITH AN INTRODUCTION BY

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TWENTY-SEVEN ILLUSTRATIONS

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TO MY FRIEND AND CONFRERÉ

JAMES WOOFFENDALE INCHES, M.D.,

WHO, BY MANY ACTS OF KINDNESS AND
WORDS OF ENCOURAGEMENT, DID MUCH
TO ASSIST ME IN MY STUDENT DAYS
AND EARLY PROFESSIONAL CAREER

THESE PAGES ARE AFFECTIONATELY
DEDICATED BY THE AUTHOR

PREFACE.

There is little doubt that the eradication of malaria is the most serious problem that confronts the sanitarian in all tropical and sub-tropical countries. The completion of the Panama Canal will forever be a monument to progressive sanitation which the American people may point to with pride. Under the splendid generalship of Colonel W. C. Gorgas, malaria and other tropical diseases have been successfully coped with, some to the point of complete eradication, others to such an extent as not to seriously interfere with the mechanical work incident to the building of the Canal. The most important disease in the latter category is malaria.

It is doubtful if there is any disease as easy to diagnosticate as malaria, if proper attention be paid to diagnostic methods, or if there is any that responds as surely to treatment, if proper treatment be instituted; for it must be remembered that quinin is one of a very few therapeutic specifics in our possession.

The author believes that one of the most sacred duties the general practitioner in malarial regions owes to the community in which he lives, is his assistance in the eradication of malaria, and inasmuch as he considers that one of the most if not the most important prophylactic unit to be the early recognition and proper treatment of the disease, especial attention has been given in the following pages to diagnosis and treatment.

It has been with the view of presenting the subject in a practical manner that this work has been written, and it is the earnest hope of the writer that he has not entirely failed in doing this.

The literature has been carefully reviewed and the author has not hesitated to make extensive quotations where he considered they were of especial value; in every instance proper recognition has been given the original author—if there are any exceptions it has been through error.

The author wishes especially to acknowledge his indebtedness to the writings of Sir Ronald Ross, Doctor Charles F. Craig, and Doctor William H. Deaderick. He wishes to express thanks to Doctor Craig for the use of many of the photomicrographs used

in illustrating the text, and for other courtesies; to Doctor Joseph Y. Porter for the cuts illustrating the various species of mosquitoes; to Doctor Hiram Byrd for many valuable suggestions in the preparation of the manuscript, and to others who have in many ways been of assistance in the preparation of this work.

G. E. H.

Jacksonville, Fla., June, 1913.

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GLOSSARY.

Anopheles, a genus of the sub-family Anophelinæ, all of which are capable of transmitting malaria.

Anophelinæ, sub-family of mosquitoes, certain of which are capable of transmitting maleria.

Asexual cycle, the cycle of the malaria parasite occurring in man.

Crescents, the sexual forms of the malarial parasite seen in the estivo-autumnal infections.

Flagella, the male sexual forms.

Gametes, sexual forms of the parasite.

Halteridium, the parasite of malaria occurring in birds.

Human cycle, the cycle of the malarial parasite occurring in man.

Macrogametes, the female sexual forms.

Merozoites, the organisms resulting from the sporulation of the Schizont.

Microgametes, same as flagella.

Microgametocyte, a male gametocyte.

Mosquito cycle, the cycle of the malarial parasite occurring in the mosquito.

Oöcyst, the organism evolving from the oökinete.

Oökinete, the organism evolving from the fertilized macrogamete.

Parthenogenesis, reproduction without fertilization.

Schizogony, the evolution of the parasite in man.

Schizonts, the asexual forms of the parasite.

Sexual cycle, the cycle of the malarial parasite occurring in the mosquito.

Sporoblasts, spherical bodies seen in the oöcyst, finally evolving to sporozoites.

Sporogentic forms, the various forms seen during the cycle of the parasite in the mosquito.

Sporogony, the evolution of the parasite in the mosquito.

Sporonts, same as oöcyst.

Sporozoites, small organisms the final product of sporogony with which mosquitoes transmit malaria to man.

Sporozoa, the class of parasitic protozoa including the malarial parasites.

Trophozoite, the young form of the parasite seen after the merozoite enters the red cells.

Zygote, same as oökinete.

INTRODUCTION.

BY CHARLES C. BASS, M. D., NEW ORLEANS.

It gives me great pleasure to write a short note of approval and commendation of this book after carefully reading the proof. Malaria is just at this time attracting special attention of the medical profession and of others. Other countries are taking up seriously the eradication of the disease. Its prevalence to the present extent is a discredit to the intelligence and progressiveness of the American people. There are indeed few diseases which could be so easily prevented and for which we have so perfect a specific. Every year the South pays her tribute of thousands of lives to this preventable and curable disease, to say nothing of the suffering, inefficiency and loss of millions in wealth. The development of this great section of the country has been held in check mainly by three diseases—yellow fever, which broke out at intervals, setting the whole country in panic, and leading to that destroyer of commerce, shotgun quarantine; hookworm disease, which insiduously sapped the very life-blood of millions of the youth of the country; and malaria, which perhaps takes greater toll than either. Through a clear understanding of the disease, yellow fever has gone, never to return in epidemic form. Hookworm disease is rapidly being eradicated by the combined efforts of the State Boards of Health, the Rockefeller Hookworm Commission, and the medical profession. But malaria continues little checked mainly for lack of sufficient knowledge on a subject as simple perhaps as either yellow fever or hookworm disease.

The appearance, therefore, of this work at this time is indeed fortunate. It is written for the general practitioner by a man whose experience and research in this disease for many years in one of the most intensely malarious sections of the United States enables him to view the subject from the most practical standpoint.

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MALARIA.

CHAPTER I.

GENERAL CONSIDERATIONS.

DEFINITION.

Malarial fever is a disease produced by specific organisms, belonging to the class *Sporozoa*, genus *Plasmodium*, which penetrate and occupy the red corpuscles, destroying those they occupy, and producing an anemia, which is accompanied by an enlargement of the spleen and other pathologic lesions. The disease is characterized by a periodicity in its clinical symptoms concomitant with the sporulation of the organisms which occurs at definite intervals, depending on the species of plasmodia, these being the benign tertian, the quartan, the estivo-autumnal tertian, and the estivo-autumnal quotidian, all of which can be differentiated by variations in their morphology. The fever accompanying the invasion may be remittent, intermittent, or continuous, and may or may not be preceded by chills or followed by intense sweating. The disease is transmitted by certain mosquitoes belonging to the Anophelinæ group and can be contracted in no other way. All forms of the disease, in all of its stages respond to the quinin salts if properly administered.

HISTORICAL.

The disease was given its name by Torti, who, in 1753 A.D., wrote a very thorough and exhaustive work on the subject, in which he classified the various forms. It was given the name *mal aria*, meaning bad air, in view of the popular idea that the infection was contracted by inhaling miasmatic odors common around swamps and marshlands.

The history of the infection is a complete one and has its beginning at a period even antedating the Christian era. Deaderick states that the disease is mentioned in the Orphic poems, both the quartan and tertian types being alluded to, this a thousand years before Christ. Hippocrates wrote on periodic fevers, dividing

them into quotidian, tertian, subtertian, and quartan. Galen, Cicero, Varro, Levy, and Celsus also described periodic fevers, and in the days of the Roman Empire when the ravages of the disease were at a very high point, there were extensive drainage schemes, as described by Celli, consisting of large aqueducts, showing that the sanitarians of those days were upon the right track, even if they were largely working in the dark. Craig in speaking of this work considers, as evidence of the success of these operations, the fact that districts then having populous and thriving cities, since gone to ruin, are now uninhabitable as a result of the pernicious forms of malaria that prevail. It is impossible to say, however, to what extent malaria may itself be responsible for the very existence of these ruins, for it has often been claimed that the fall of the Roman Empire was in certain measures due to the undermining influences of this disease.

Leaving behind us the Middle Ages, noted for its days of darkness and superstition and all that such implies, and during which, as might be expected, little if any knowledge was attained concerning the disease, we come to the year 1640 in which the Countess Chinchon introduced cinchona into Europe. This drug was originally studied by La Condamine in the province of Loxa, and named by him "quinquina" in the year 1737, and in 1741 Linné proposed a new name, "cinchona," in honor of the woman who had introduced it. The use of this drug, which has since proved a specific in malarial fevers, was bitterly opposed for many years by certain religious bodies, and in Rome, a veritable hotbed of malaria, it was not used until nine years after its introduction, at which time the Jesuits began to use it extensively. Following the introduction of quinin we find a slow but steady advancement in knowledge concerning the disease. Morton had, in 1697, described the simple and pernicious forms and was enthusiastic in his support of treatment with cinchona. Lancisi, in 1717, suggested that the infection may be transmitted by mosquitoes, being probably the first to express such an opinion. Torti, in 1753, in his paper already referred to, gave an exhaustive description and classification of its various forms. Meckel, in 1847, was the first to describe the pigmented leucocytes, a familiar picture now in the study of malarial blood. In 1849, Mitchell's theory that certain spores existing in marshlands are the etiological factor received much credence, and secured increased favor when Salisbury, in 1866, connected the

spores of *Palmella* with the etiology. These spores he found in numerous quantities on the banks of the Ohio and Mississippi rivers, and he thought at the time that he was able to demonstrate them in the urine of patients suffering with malaria. When Klebs and Tommasi Crudeli, in 1879, announced the discovery of what they named the *Bacillus malariæ*, which they found in the mud of marshy districts wherever malaria was rampant, and were able to reproduce them by culture methods, producing the symptoms of a malarial infection when injected into man's circulation, it was generally considered by the medical world that at last the organism causing the infection was isolated.

The following year Laveran, an army surgeon in the French Service, announced, through the Academy of Medicine in Paris, the discovery of parasites in the blood of people suffering from malaria. This announcement marked an epoch in the history of the disease and was an event of the greatest importance occurring in medical circles for generations. His descriptions covered the crescentic forms of the estivo-autumnal infections and also the flagellated forms, which were described by him as being hyaline bodies containing much pigment, and from which protruded hyaline filaments which gave to the organism ameboid movement; it was this form of the parasite that put beyond any doubt in his mind the fact that they were true parasites—to quote his own words: "From then on I had no further doubt as to the parasitic nature of these elements which I had found in the blood." His announcement, which was followed a year later by a more extended report, did not meet with the consideration that such an important discovery merited, and it was not until the year 1885 that much attention was paid to his words. In 1882 Richard, a confrère of Laveran in the French Army Service, confirmed the discovery and described the young ring forms of the parasite, and, in 1885, Marchiafava and Celli came forward and also confirmed Laveran's original findings. The confirmation by these authorities resulted in much scientific interest, for these two men, whose opinions were highly held, had until that time strongly upheld the theory of Klebs and Tommasi Crudeli that the origin of the disease is bacterial in nature. The following year the true nature of the malarial organisms was definitely established and accepted throughout the medical world, many observers confirming the findings of Laveran. In the same year Golgi associated the periodicity of the

fevers with the sporulation of the parasites, and this has since been confirmed by Osler and many others. Later work, which will not be discussed here in detail, resulted in a complete knowledge of the morphology and biology of the various parasites throughout the cycle both in man and in the mosquito.

This discovery of Laveran made possible the diagnosis of malaria from other fevers by more certain and satisfactory methods than the mere fact of a fever's responding or failing to respond to the action of the quinin salts, and attention was now directed to the mode of transmission. The theory of insect transmission had at various times been suggested, but no definite investigation had been carried on. During more recent years King in 1883, Koch in 1884, Laveran in 1884, Flügge in 1891, Manson in 1894, and Bignami in 1896 had all advanced and supported the theory.[1] But it was the hypothesis of Manson, advanced in his Goulstonian lectures, and his direct suggestion, that was responsible for Ross, in 1895, going into research work to establish it as a fact. His work, which was most painstaking and thorough, aroused for him the admiration of the scientific world and resulted in his being able to demonstrate beyond all doubt that certain mosquitoes are necessary for the transmission of the parasite; that these insects act as the intermediary host, allowing certain processes of evolution to take place; and that the body of the insect is the natural habitat for the development of this evolution which can take place in no other way.

In 1898, MacCallum completed the chain of knowledge that had taken all these years to accumulate, and by his studies and observations of the sexual forms of the parasite determined that the flagellated forms become detached from the parent body and penetrate the female organism, resulting in its fertilization. After studying this process in the *Anopheles,* he determined that it takes place in the stomach of the insect, and is analogous to the cycle taking place in the *Culex* with the *Halteridium.* His observations have since been confirmed by numerous observers.

Bignami, in 1898, was the first to produce the disease by inoculating a person with no previous history of malaria. This was followed by numerous inoculations from mosquito to man. In 1899, Bastianelli, Bignami, and Grassi infected mosquitoes with

[1] It may be mentioned in passing, as an interesting historical fact, that at this juncture Smith and Kilborne, of the Bureau of Animal Industry, Washington, established the fact that Texas fever in cattle is transmitted by ticks.

the gametes of a quartan infection, and followed the evolution of these forms to that of the sporozoite.

The detailed story of the discovery of Ross that the mosquito is the transmitting agency, how it was later demonstrated in various ways, such as a number of people living in the Roman Campagna in exactly the same manner as the natives, with the single exception of adequate mosquito protection, thereby saving themselves from infection, while the unprotected natives all became sick; how Manson further demonstrated the correctness of the theory by importing from Italy infected mosquitoes and producing the infection in his own son and another gentleman in London; and various other experiments, together with the investigations carried on by many observers concerning the life cycle of the parasites in the mosquito, have brought the question of transmission to a point of accepted fact. The application of this knowledge in the extensive work done in Panama, and other points, in the eradication of malaria, completes the history of the disease.

GEOGRAPHICAL DISTRIBUTION.

Malaria while classified as a tropical disease is by no means one that is confined to tropical or subtropical countries. The method of transmission is such that conditions necessary for its propagation are prevalent to a greater degree in the warm climates than in the cooler ones. The disease prevails on every one of the continents, increasing in extent and severity as the warmer portions are reached; but while the estivo-autumnal and quartan infections are more closely confined to warmer latitudes in both hemispheres, this being more especially marked of the estivo-autumnal than of the quartan type, the benign tertian infection can be seen in almost any latitude below 60 degrees.

North America.—In North America the disease is endemic in certain portions of all of the Southern states, those known as the Gulf states being especially badly infected. The estivo-autumnal tertian variety is very common in certain parts of Florida, and the quotidian form is present, but not so often encountered. The author has known as high as 80 per cent of the population in certain portions of this state to become infected in a single season, while the disease is endemic to the point that, in certain localities at least, 25 per cent are annually attacked. Georgia, Texas, and certain parts of South Carolina are also heavily infected with both

the estivo-autumnal and benign tertian types. Along the Mississippi River toward its southern course estivo-autumnal malaria is very prevalent and especially severe, resulting in many fatalities. The disease is quite common in Missouri, Oklahoma, Arkansas, and Kansas; present, but less frequent, in North Carolina, Virginia, West Virginia, and Maryland. In the New England states the tertian infection is very often seen, but the more severe forms are seldom encountered; while in the Middle Western states the tertian variety is often observed, and occasionally estivo-autumnal types occur. A few years ago the latter was reported quite prevalent in certain portions of Indiana, and there are sections of Michigan, Ohio, Illinois, Minnesota, and Wisconsin that still have tertian malaria of the benign form to deal with. Passing through the Western states and approaching the Pacific Coast, the disease becomes less frequent, but it is more or less prevalent in Washington along the Puget Sound and Columbia River. Portions of Oregon remain infected, and in some parts of the state of California all forms of the disease are frequently seen. Canada is practically exempt, with the exception of that part of her southern border touching on the Great Lakes.

Mexico and Central America are badly infected, and the disease has numbered its victims by thousands. Panama, especially severely infected with the estivo-autumnal types in the past, is now enjoying the benefits of a continued campaign in that portion known as the Canal Zone, where active measures against the mosquito, together with protection afforded the employees by screening and the prophylactic use of quinin, has resulted in a very marked reduction in both mortality and morbidity from this cause, together with a general improvement of health conditions, showing to the world in a striking manner what can be accomplished under even the most unfavorable conditions where proper measures are consistently carried out.

South America.—All of South America is severely infected to a greater or lesser degree, some portions being uninhabitable on account of the malignancy of the infections. Peru, the Argentine Republic, and Uruguay are exceptions to the rest of the continent, the infection in these countries in any of its forms being rather rare.

West Indies.—The West Indies still harbor the disease to a point of great severity both in its prevalence and in its malignancy, tak-

ing on its most dangerous forms in Cuba. Porto Rico is nearly free from the severe types, the benign tertian being the form generally seen; while St. Vincent and the Barbadoes are said to be practically free from any of the malarial infections.

Europe.—At one time Great Britain was quite severely infected, but the disease is now extinct, in spite of the fact that *Anopheles* are present. This phenomenon has been quite generally discussed by modern writers; Manson suggested the possibility of the insects feeding on some vegetable juice poisonous to the parasites, while Samson considered the possibility of the existence of hyperparatism: that is, the presence of some other organism that destroys or interferes with the development of the malarial parasite in the body of the mosquito. It is, however, more than probable that the extinction has gradually been brought about by the reduction of gamete carriers among the inhabitants of those islands, together with the fact that although *Anopheles* are present they are not in great numbers.

On the European continent malaria is widely distributed. France, Germany, Holland, Belgium, Spain, and Portugal are all more or less severely infected with the benign tertian, while Italy, Greece, Sicily, and Turkey have suffered from the ravages of the disease to a maximum for many centuries, all forms of the disease being present. In Sweden and Denmark occasional cases are seen, but Norway is practically exempt.

Asia.—Asia presents many zones of infection, India being very severely infected, the disease costing the English government an immense sum annually, and the country a death toll of a million lives in what they term an ordinary malarial year, while there are some years during which an exacerbation of the disease results in four or five million deaths. The infections are also seen in the lowlands of Japan, and in the Philippine Islands they are especially severe, the estivo-autumnal types being very prevalent. In the years 1900–1901, along the Cauayan River, in the upper part of the province of Luzon, fully 50 per cent of our military force was infected, many fatalities occurring.

Africa.—On the west coast of Africa the most intense infections are seen, and the malignant types are common along the Congo and Nile rivers. The islands of Madagascar and Mauritius are also badly infected.

Australia.—The disease occurs along the entire coast of

Australia, but the interior of the country is comparatively free.

It is seen by the above review of the geographical distribution that malaria covers practically the entire surface of the globe. It has been claimed that it has reappeared in America of late years as the result of troops returning with the infection contracted while serving on our island dependencies, in sections where it had become practically unknown. Craig cites an instance occurring in a city in Connecticut, where some years before the Spanish-American war occasional cases of benign tertian malaria only were observed. Following the return to this city of a company of militia, several residents, who had not been away, developed estivo-autumnal malaria, which was traced to the returning soldiers, several of whom had suffered with such attacks while serving in Cuba; and this illustrates how an infection of this nature can develop following the importation of gamete carriers. The *Anopheles* were present all the time, some few carriers of the benign tertian gametes kept that infection alive, but during a period of many years no cases of estivo-autumnal infections had occurred until this type was introduced following the return of these soldiers, some of whom harbored the crescentic forms.

ECONOMIC LOSS.

An estimation of the immense loss attributable to malaria throughout the world is impossible of anything even approaching accuracy, but we can gather enough to show that every possible effort should be put forth against a disease that is so easily within our power to eradicate.

Celli shows that the economic loss to Italy has been an enormous one. In addition to that incurred as a direct result of malarial infections, he claims that the existence of the disease has been responsible for large tracts of land remaining uncultivated, owing to the fact that the territory was uninhabitable on account of the prevalence and the intensity of the malarial infections. He sums up the situation with the statement that "Malaria annually costs Italy incalculable treasure."

Leslie estimates the mortality in India from this cause at 1,130,000 annually "in an ordinary malarial year—and as in such a year it is not a very fatal disease, this number of deaths represents an enormous amount of suffering and loss of labor, often at a time when labor is of most value."

Ricchi calculates that the Adriatic Railway Company alone, for 1,400 kilometers of railway and for 6,416 workmen in the malarial zones, spends on account of malaria the enormous sum of 1,050,000 francs a year.

Taking as an estimate the number of deaths attributable to malaria in the registration area of the United States, which has for the past many years exceeded a thousand, admitting a mortality rate of one per cent (which is high), we can account for a hundred thousand cases annually; and when we take into consideration the fact that these figures do not include the rural population and only a very small proportion of the city populations of the Southern states (these not being represented in the registration area, owing to inefficient regulations concerning the recording of their vital statistics), and that it is in this portion of our country that most of our malaria prevails, it can be seen at a glance what, even at this day, malaria means to the American people. The loss of time to the wage-earner, the care of the sick, and the necessary expenditures for medical attendance and drugs will run the total into millions of dollars every year, and Howard has even estimated this total as being $100,000,000 annually.

With such figures before us, and the knowledge we have of what has been accomplished wherever a consistent campaign has been instituted against the malarial infections, it would appear that the time cannot be far distant when the matter of the eradication of the disease will be taken up seriously by legislative and administrative bodies.

CHAPTER II.

ETIOLOGY—THE MALARIAL PARASITES.

With Laveran's discovery that the disease is produced by specific organisms, Manson's and Ross' work showing conclusively that these organisms are carried and injected into the human circulation by certain forms of mosquitoes, MacCallum's elucidation of the significance of the gametes in the circulation of man, and the later rôle enacted by them in the body of the mosquito, it is definitely established that two requisites exist in every malarial district, each harmless in the spreading of the disease without the aid of the other. These are: (1) certain mosquitoes, members of the Anophelinæ group; and (2) man, who may or may not have had acute clinical manifestations of the disease, but who harbors in his circulation the sexual forms of the parasite. The mosquito cannot originate or produce an infection, but must first become infected itself, by feeding on the blood of man whose blood contains the sexual forms of the parasite. The sexual cycle cannot proceed in the blood of man, but commences as soon as the sexual forms reach the stomach of the mosquito, when after a certain time the evolution of the parasite reaches the sporozoite stage, these forms becoming lodged in the salivary gland of the mosquito where they remain until they again reach the human circulation during the biting process of the insect.

Conditions, therefore, which favor the breeding of mosquitoes increase the likelihood of malarial infections being present in a locality, and as heat and moisture are necessary requirements for their propagation, it follows that the disease will be more prevalent in tropical and subtropical countries than in the more temperate zones. It is not, however, confined to the tropics. The march of civilization will in the natural order of events eliminate the disease in most temperate climates, while in the warmer ones the infection will remain endemic on account of the peculiar conditions favorable to mosquito life, which in many instances are hard to meet, or, at all events, the meeting of such conditions would involve the expen-

diture of immense sums of money, for which, up to the present time, the public have not been educated to the point of seeing the necessity. In the warmer climates the disease while endemic will be marked by exacerbations that depend on meteorological and certain other conditions. An example of what the natural trend of civilization will do toward the elimination of malaria, without any special attention being paid to the matter, is its disappearance from many portions of our Middle Western, and certain of our Eastern states, where at times in the past it was very prevalent, but is now practically extinct. In a great deal of this territory thirty or forty years ago the disease was common, but as soon as the land was cleared up, properly drained, and settled, malaria began to decrease and has slowly disappeared, without any special sanitary measures being adopted.

The work, commenced by Laveran, carried on by Manson, Ross, and others, together with the recent observations of Darling, showing that the sexual forms of the parasite are amenable to the action of the quinin salts—it being previously maintained that this drug has no action on these forms—has made possible the inauguration of a campaign that would, if consistently carried on, wipe out this infection entirely. Osler, many years ago, writing on the importance of the discoveries of Laveran and Ross, said, "One of the greatest scourges of the race is now at our command," and it is a matter of regret that with this command of the situation more has not been accomplished toward the eradication of a disease that results in so much suffering.

It is safe to say that, if the mortality rate were higher than it is in most sections where malaria prevails, greater advancement would have been made in the past decade toward its complete eradication than has been the case. That "familiarity breeds contempt" never had a better illustration than is seen in the attitude of the people at large in malarial districts. Even among the educated and in those who believe in the mosquito transmission of the disease, this indifference displayed toward possible, and in many instances probable, infection is very appalling and a matter of discouragement to the sanitarian in malarial sections. Little attempt is made to guard against infection, which results in the presence of malaria in many places, where, by a very little individual prophylactic work, it could be stamped out very easily in a short time.

In striking contrast to this condition stands out the very successful elimination of yellow fever from the United States, and foreign dependencies, and an illustration of the possibilities of a campaign against malaria is seen in the marked reduction of this disease together with yellow fever in Havana. Gorgas states that, in 1900, the year before active work against the mosquito was commenced, there occurred in that city 325 deaths from malaria; during 1901, the year that work was commenced, there were 151 deaths from this cause; in 1902, 77; and in 1903, the mortality from malaria reached the low figure of 45.

CLASSIFICATION OF THE MALARIAL PARASITES.

There have been many classifications of the malarial plasmodia proposed by various writers on the subject, and a number of descriptions of the species, and while they are all of interest to the zoölogist, a lengthy discussion of them would be of little practical interest to the general practitioner. The classification suggested by Craig is a complete one, and will be followed to the exclusion of others in the following pages.

The classification is as follows:

Division—Protozoa.
Class—Sporozoa.
Order—Hæmosporidia.
Genus—Plasmodium.
Species—

1. *Plasmodium malariæ* (Marchiafava and Celli). Quartan malarial plasmodium.
2. *Plasmodium vivax* (Grassi and Feletti.) Tertian malarial plasmodium.
3. *Plasmodium falciparum* (Blanchard). Estivo-autumnal plasmodium, tertian type.

Subspecies—

4. *Plasmodium falciparum quotidianum* (Craig, 1909). Quotidian estivo-autumnal plasmodium.

Before taking up in detail the morphology, biology, and staining qualities of these various species, a brief description will be made of the cycle of evolution that takes place in man's circulation, and that occurs in the body of the mosquito, common to all of the species.

There are two distinct forms of evolution necessary for the continuation of the life of these organisms, each complete of itself, but nevertheless depending on the other. One takes place in the blood of man, is of an asexual nature, termed schizogony; the other in the body of certain species of mosquitoes, is of a sexual nature, and termed sporogony. Ross, Marchiafava, Grassi, MacCallum, Celli, and others have carefully studied the forms undergoing evolution in both the human and mosquito cycles. The observations of these workers have been confirmed by all who have studied the morphology of the parasites.

SCHIZOGONY.

The zoölogical terms applied to the forms of the parasite observed in schizogony are the schizont, the merozoite, and the trophozoite. The schizont is a common term applied to all asexual forms resulting from the sporozoite injected by the Anophelinæ in her saliva, in the biting process, and those asexual forms resulting from the merozoite. The merozoite is that form which results from the sporulation of the fully grown schizont, and which re-enters the corpuscle to continue schizogony. The trophozoite is the young hyaline form that develops following the penetration of the corpuscles by the sporozoites and the merozoites. These forms are not seen in the mosquito and until their successful cultivation in vitro by Bass were not known to develop outside the human body. The schizonts are thin bodies resulting from the injection of sporozoites from the mosquito and from the merozoites, the product of sporulation. Sporozoites are needle-shaped forms that penetrate the red corpuscle and immediately assume ring shapes, these being termed trophozoites. At first non-motile, they gather pigment from the hemoglobin assimilated, gradually assuming activity, which increases up to a certain age of the parasite, after which it decreases. Depending on the species, they then assume various shapes and develop certain differential points in their morphology, and as development proceeds the corpuscles, occupied, undergo certain changes, also depending on the variety. Reaching the sporulating stage the corpuscle is destroyed; the full-grown plasmodia are divided into a number of spores; these spores known as merozoites, re-enter the red corpuscles, and the evolution is once more under way. This cycle is completed in twenty-four, forty-eight, or seventy-two hours, depending on the species,

hence the terms quotidian, tertian, and quartan malaria. The author has found that a certain amount of confusion has arisen among students from the terms tertian and quartan malaria. In the former, while the cycle of the parasite is completed within forty-eight hours, the resulting chill takes place every third day, and on this account the name tertian has been applied, but it should be clear in the minds of all that the cycle does not take three days for its completion. Thus a chill taking place on Monday is followed by another on Wednesday, or the third day, the cycle of the *Plasmodium vivax* (tertian malaria) being completed in forty-eight hours. So, also, in the quartan type, the cycle of the *Plasmodium malaria* is completed in seventy-two hours, but results in a chill, or exacerbation, every fourth day.

FORMATION OF GAMETES.

While the cycle known as sporogony takes place in the mosquito, the sexual bodies, or gametes, as they are called, originate in the blood of man. They are known as macrogametes (female), and microgametocytes (male), but while formed in the blood of man, are incapable of further development in the human circulation. Although the development of a microgametocyte to that of a fully formed microgamete is part of the cycle that takes place in the mosquito, and will be described in discussing the forms of evolution that take place in the body of this insect, this phenomenon may under certain conditions be observed in human blood, but only after it has been withdrawn from the circulation.

It has been a debated question whether gametes result from a separate class of sporozoites specifically intended for gamete formation, or whether the sporulating forms resulting from schizogony, by the action of the human host, cause certain of the merozoites to assume gamete formation. The latter theory is the one that is now generally accepted. Craig writes, "I believe with Schaudinn that the gametes are produced only after the plasmodia have undergone sporulation for some time, and that, therefore, they are of human origin, being differentiated during the process of schizogony, and not introduced as such by the infected mosquito. In other words, all of the sporozoites introduced by the insect develop into schizonts, the gametes or sporonts developing from a schizont after a certain period of time, some of the merozoites being thus differentiated."

EXPLANATION TO PLATE

SCHIZOGONY—The mosquito (A) in biting man injects sporozoites (1) which immediately upon entering the circulation assume ring forms (2); as evolution advances the young schizont (3) is formed which gradually enlarges as evolution proceeds (4). Toward the end of the human cycle the sporulating form (5) is seen, which in turn produces a number of merozoites (6). Each of these young merozoites (7) now re-enter other red cells (follow $\xrightarrow[a]{}$) and, repeating the process begun by the original ring form (2), continue schizogony indefinitely; thus multiplying the number of parasites by many times every sporulating period.

SPOROGONY—However, after schizogony has continued for a certain number of days, certain of the merozoites undergo a transformation evolving to sexual forms known as the macrogamete or female (8) and the microgametocyte or male (9). Neither of these forms can proceed further in the process of evolution so long as they remain in the circulation of man, but as soon as they are ingested by the mosquito (B) evolution is again under way (follow $\xrightarrow[b]{}$). The first change that occurs is that of flagellation of the microgametocyte which results in the formation of the flagellate body (10), which in turn produces the fully developed microgamete (11). This form now penetrates and fertilizes the female form (12) resulting in a body which lodges itself in the muscular walls of the mosquito's intestine and known as an oökinete (13) which later evolves to the oöcyst (14) from which evolve the sporozoites (15), these becoming lodged in the salivary glands and being free in the saliva of the mosquito with which they are injected by the insect into man's circulation (as shown at 1)—the cycle being thus completed.

NOTE: There is no attempt in the foregoing to follow each and every stage of evolution that takes place in the circulation of man or in the body of the mosquito, it being the aim to simply bring out the salient points that take place in the evolution of the parasite.

CYCLE OF THE MALARIAL PARASITE IN MAN AND THE MOSQUITO

A. Mosquito Injecting (1) Sporozoites.

2. Young ring form.
3. Young schizont.
4. Older schizont.
5. Sporulating plasmodium.
6. Young merozoites.
7. Merozoite, continuing process of schizogony.
8. Macrogamete (female sexual form).
9. Microgametocyte (male sexual form).

B. Mosquito becoming infected with the sexual forms while feeding on blood of infected man.

10. Flagellate body.
11. Microgamete.
12. Microgamete fertilizing female.
13. Oökinete.
14. Oöcyst.
15. Sporozoites.

SPOROGONY.

After the mosquito has taken a meal of fresh blood from a man infected with malaria, containing the sexual forms of the parasites, both macrogametes and microgametocytes, the first form of evolution takes place in the male, consisting of exflagellation. This is a process in which the microgametocyte throws out long thread-like filaments, numbering from one or two to eight, and measuring in length from two to four times the diameter of the parent body from which they are given off and detach themselves. These filaments become actively motile, and the remaining body undergoes degeneration. This process of exflagellation, normally occurring in the body of the mosquito within half an hour from the ingestion of the infected blood, can be observed, as mentioned previously, in the human blood *after its being withdrawn from the circulation*, by carrying out the following technic, given by Cabot:

"Cut an opening one half by one inch in a piece of thick blotting paper and moisten the paper in hot water. Spread two glass slides rather thickly with fresh blood, lay the blotting paper on one side, cover the cut opening by the other, specimen side down, and slip a rubber band about both. After fifteen or twenty minutes the slides and paper may be separated, and the two specimens dried."

The slides may then be examined without staining if desired, but the flagellated bodies stain readily and are then more easily detected by those not perfectly familiar with them. The staining method will be described in the pages devoted to the staining of the various forms of the plasmodia. It should be fully understood that this process of exflagellation does not take place in the circulation of man under any circumstances and normally only occurs in the stomach of the mosquito.

Flagellation having occurred in the stomach of the mosquito, these actively motile thread-like bodies, or flagella, the fully developed microgametes, rapidly dance around until they come in contact with the female gamete, which they penetrate and fertilize, resulting in an oval body known as a zygote. This oval form soon becomes elongated, and becomes situated in the muscular walls of the mosquito's stomach, being then known as an oökinete, a motile protoplasmic body, containing pigment, with a chromatic mass, the nucleus, seen in the center, this developing into what is known as an oöcyst. This has a diameter of about 7 microns, which rapidly

enlarges, finally reaching from four to eight times its original size, containing within it the fully developed sporoblasts. From the external layers of these, develop the sporozoites, thin elongated needle-shaped filaments, which find their way to, and become imbedded in, the salivary glands of the insect. Later on, the ducts of this gland will be found to contain these bodies, being also free in the saliva, with which secretion they are injected into the blood of man by the insect, in the biting process. These glands are capable of harboring thousands of these filaments, the number injected at a single feeding being from a few to many hundreds.

To recapitulate the evolution stages of the two cycles, gametes forming in the human circulation are withdrawn by the mosquito when biting, and by a series of stages of development in this insect, sporozoites are formed, which become lodged in the salivary glands, and are injected by the mosquito into the blood of man. These penetrate the red corpuscles, and by another series of changes of development in man, reach maturity and sporulate in certain fixed periods, depending on the variety; but this series of stages of development does not end the cycle in man, for the merozoite, the product of sporulation, now re-enters the red corpuscle, continuing the cycle by schizogony. After this has taken place for some days certain of the merozoites go on to the formation of gametes, which are then ready to be taken up by the mosquito, and the cycle of sporogony repeated in this insect. The question is often asked, "if man gets the parasite from the mosquito, and the mosquito gets the parasite from man, where did the parasite originate, or which had the infection first?" As Ross says, this is like the question, if the egg comes from the hen, and the hen from the egg, which came first? All we know is that the parasite does alternately occupy man and the mosquito, that in this way are the species perpetuated, that, so far as we know, man and the mosquito are the only necessary factors for their perpetuation, and that they are unable to reproduce except under this alternation of hosts.

DESCRIPTION OF THE MALARIAL PLASMODIA.

Tertian Malaria (Plasmodium Vivax, Figs. 1–5).—This organism completes its human cycle (schizogony) in forty-eight hours, producing the typical "chills and fever," with an exacerbation of clinical symptoms occurring every third day. All stages of the development of this organism may be observed in the peripheral

blood, although sporulation takes place principally in the circulation of the viscera and that of the deep tissues, and they are more easily recognized than any of the other species, and should for this reason be chosen for primary study by the novice working with malarial blood. It is a benign infection, and the common one of temperate climates, but is also prevalent in tropical and subtropical countries.

The sporozoite having penetrated the red corpuscle, the young parasite is seen as a small hyaline protoplasmic ring (Fig. 1), measuring 1.5 to 2 microns, of low refraction, and barely distinguishable. It is at first a non-motile body, but takes on ameboid movement

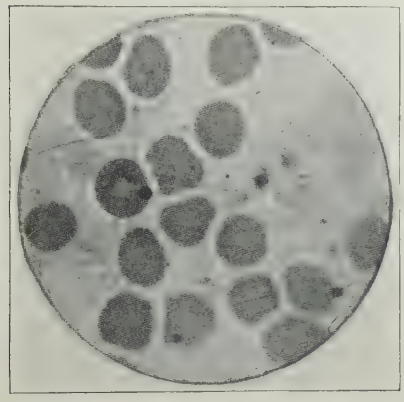

Fig. 1.—Plasmodium vivax (Tertian plasmodium). Young ring forms.

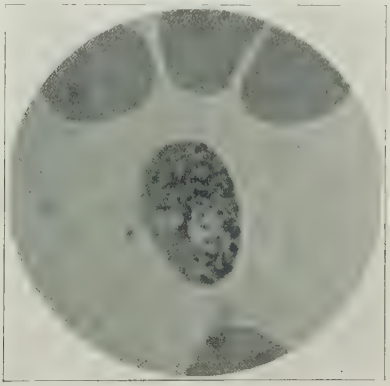

Fig. 2.—Plasmodium vivax (Tertian plasmodium). Half grown parasite. (After Craig.)

within a few hours, when fine pigment granules of a reddish-brown color form, being derived from the hemoglobin, and distributed throughout the protoplasm; and as the organism develops it takes on various irregular shapes, the activity of the pigment granules, which is very pronounced, being responsible for this. Minute pseudopodia may be observed rapidly pushing out and withdrawing themselves; with the growth of the parasite motility increases, and the organism is seen to frequently change its position in the corpuscle; the pigment granules increase, continue actively motile, and in the fresh specimen may be observed dancing around. At the end of twenty-four hours the plasmodium occupies fully half of the red corpuscle (Fig. 2), which by this time has increased fully two-thirds over its original size; ameboid motion decreases, and

twelve hours later has practically ceased, the pigment remaining active. In a few more hours, or four or five before the completion of the forty-eight-hour cycle, the pigment collects at or near the center of the fully grown organism, while the protoplasm is seen to be dividing in a radial manner (Fig. 3), resulting in the formation of from twelve to twenty-four ovoid bodies or spores, merozoites, which are arranged in two irregular circular rows, one within the other. (Fig. 4.) By this time the corpuscle is hardly visible, only a very pale and faint outline of the cell being seen, and even this soon disappearing, the red corpuscle being destroyed and sporula-

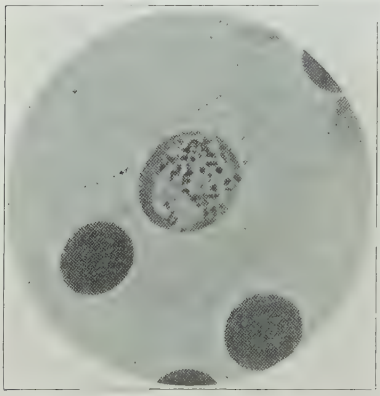

Fig. 3.—Plasmodium vivax (Tertian plasmodium). Presegmenting parasite. (After Craig.)

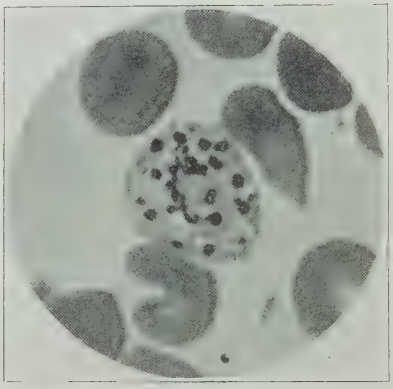

Fig. 4.—Plasmodium vivax (Tertian plasmodium). Segmenting tertian parasite. (After Craig.)

tion completed. The young merozoites now penetrate other red (Fig. 5) cells, to go through the same process, continuing the cycle of schizogony for more or less indefinite periods, depending on the resistance offered by the infected individual, and the treatment instituted, or both. It has always been thought that with sporulation completed the merozoites became free in the blood-plasma, but the research work of Bass and Johns, recently conducted in Panama, in connection with the cultivation of the plasmodia in vitro, demonstrated the interesting fact that the merozoites die almost immediately in blood plasma. Bass is of the opinion that the merozoites only enter the other red cells by direct contact of the cells at the time of segmentation. In a personal communication to the writer he describes the process as follows: "A parasite grows larger and larger until it finally is too large to pass

through the smallest capillary. The consistency of the substance of the parasite is quite different from that of the red cells and is very much less yielding. It, therefore, cannot change its shape very much to accommodate the capillary. It continues to grow and other red cells naturally float up against it. Finally, whenever segmentation takes place, if the opening in the infected cell occurs opposite another cell now packed against it, the young merozoites pass directly into the new red cell before they are exposed to the plasma, which is extremely destructive to parasites."

The changes observed in the red corpuscles invaded by the tertian

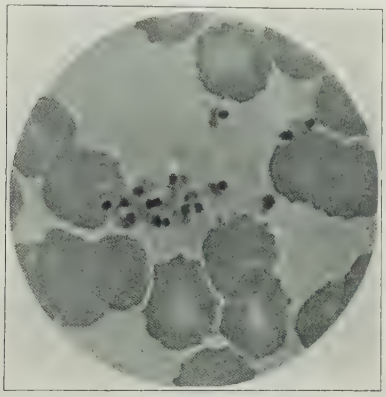

Fig. 5.—Plasmodium vivax (Tertian plasmodium). Total separation of the spores. (After Craig.)

parasite are very marked, and are sufficient in themselves to differentiate this type of infection from other forms. Soon after, the sporozoites from the mosquito, or the merozoites formed by sporulation, invade the cells, these cells immediately become distended and gradually increase in size until, by the time the parasite has assumed its full growth, they are often two or three times their ordinary size, and only a faint outline of the rim is visible. They also lose their regular contour, having been formed into all sorts of shapes by the contained parasites which assume fantastic forms on account of the activity of the pigment. The hemoglobin that forms the pigment is assimilated by the parasite, and this results in the decolorization of the corpuscle, which is seen early, as is also the increased size of the cell, so that any cells either enlarged or pale in color should be carefully scrutinized for the detection of

parasites. It is not uncommon to see a cell with a double infection: that is, one containing two young forms. This phenomenon, which is of considerable significance under certain conditions in the etiology of recurrences, will be discussed at another time.

Another important change is the formation of granules, known as Schuffner's dots, in the infected cells, producing a stippled effect, and the presence of these, plainly brought out in the stained specimen, is significant of tertian infections. Craig states that he has seen them in quartan infections, but only rarely, and considers their occurrence in these infections as of such rarity as to be of no practical importance, and that in the few quartan cases in which he has observed them it was in the older forms and in no instance with the young rings, which leads him to consider that all cases showing ring forms accompanied by Schuffner's dots are undoubtedly tertian infections.

Other changes occurring in the blood, such as reduction of red corpuscles, loss of hemoglobin, and alterations in the relative count of the leucocytes, will be discussed in considering the pathology of malarial infections.

Quartan Malaria (Plasmodium Malariæ, Figs. 6-8).—The cycle of this species of malarial plasmodia is completed in 72 hours, an exacerbation of the clinical symptoms occurring every fourth day, and concomitant, as in all types of malaria, with the sporulation of the parasites. It is not so common as either the benign tertian or the estivo-autumnal infections. The author has seen but two cases in the state of Florida, and while on duty with our troops in the Philippine Islands in 1900–1901, saw but three or four cases in a total of many hundreds of cases of malaria. Schizogony may be observed in all stages of evolution in the peripheral circulation of man, the sporulating forms of this species being encountered more frequently in the peripheral circulation than in any of the other species.

The careful observer will have no difficulty in differentiating this organism from the *Plasmodium vivax*. As first seen in the red corpuscles it appears as a small hyaline non-motile ring, being more refractive than the tertian parasite, slightly larger, and does not produce enlargement of the invaded cell, so characteristic of the organism just described. In the early pigmented forms about one quarter of the corpuscle is occupied, and as the pigment develops the parasite assumes motility, which is, however, much less pro-

nounced than in the tertian form. The pigment is much coarser than in the tertian parasite, of a dark-brown color, and much less active—it will be remembered that the pigment of the tertian organism is extremely active, being made up of fine granules and of a reddish-brown color. (Fig. 6.) At the end of twenty-four hours motility is practically absent, the protoplasm appears granular, is more distinct in outline, and the pigment tends to collect on the edges of the plasmodium, sometimes forming a circular band on the periphery of the organism, which may at this time take on triangular or oval forms.

At the end of thirty-six hours pigment has considerably increased, is non-motile, and the corpuscle, instead of being considerably en-

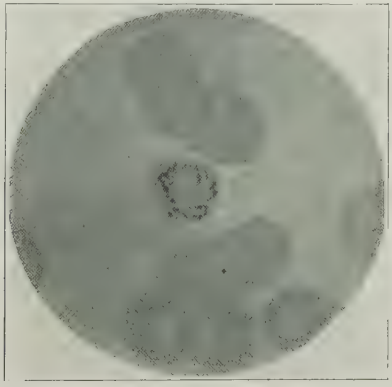

Fig. 6.—Plasmodium Malariæ (Quartan plasmodium). One-quarter-grown parasite. (After Craig.)

larged as in the tertian form, tends to retract around the parasite, which is very refractive, occupies but half or less of the cell; and there is no decided change in the organism for several hours following. From six to ten hours before sporulation, the pigment, which has collected on the periphery of the parasite, is seen to scatter throughout the protoplasm and is non-motile, and the parasite, spherical in shape, remains devoid of ameboid movement; but as the sporulation stage is neared the pigment is seen to collect in the center of the organism, while the protoplasm divides, in a similar radial manner to that seen in the tertian, forming separate and distinct bodies, the merozoites. (Figs. 7 and 8.) Another marked point of differentiation between the tertian and quartan parasites

is that, while, in the former, sporulation results in the formation of from twelve to twenty-four spores, or merozoites, arranged in two irregular circular rows, the quartan sporulating stage results in from six to twelve segments, arranged in a single circular row around the pigment body. The presporulating body generally fills the invaded cell entirely, which becomes invisible, but in some instances segmentation occurs before the whole cell becomes occupied. Sporulation completed, the merozoites enter other red cells, as in tertian malaria, repeating the schizogonic cycle, but it should be remembered that in all infections, after schizogony has gone on for a certain, at present undetermined, period, certain of the merozoites undergo a transformation to gametes, resulting in

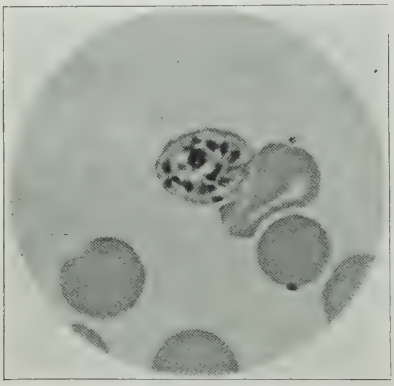

Fig. 7.—Plasmodium Malariæ (Quartan plasmodium). Presegmenting parasite. (After Craig.)

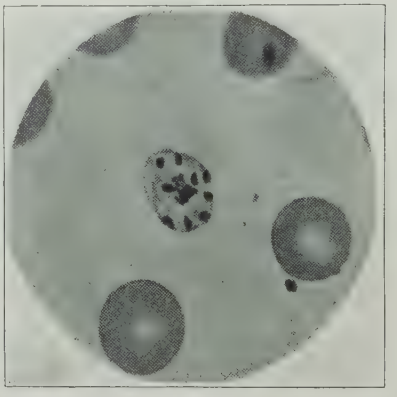

Fig. 8.—Plasmodium Malariæ (Quartan plasmodium). Segmenting parasite. (After Craig.)

the fully formed sexual organisms, which are taken up by the mosquito and undergo evolution in the body of this insect.

The changes taking place in the blood in quartan infections are as follows: The corpuscle, instead of enlarging and taking on irregular shapes, as in the tertian, becomes retracted around the parasite, is smaller, or else remains unchanged in size, and does not assume the pale color common to cells infected with the tertian parasite, but takes on a dark-green color. There is also an absence of Schuffner's dots, described in tertian infections. Craig's statement that these may occur in quartan infections has been discussed, and it will be remembered that, while in exceptional cases these dots may be seen after the organism has taken on growth and lost the ring form, they are never seen in conjunction with this form.

Tertian Estivo-Autumnal Malaria (Plasmodium Falciparum, Figs. 9-11).—This is the most common of the estivo-autumnal infections, and has been more often reported than the quotidian type. The cycle is completed in forty-eight hours, or sometimes a little less, and attended with exacerbations of symptoms every third day. Double invasion of a cell and even multiple infections are a common occurrence in this type of the disease. (Fig. 9.) The parasite as first seen is a hyaline ring (Fig. 10), usually round but occasionally taking on oval shapes, and while it is somewhat hard to differentiate from the very early forms of the quartan parasite, a close and careful observation will bring out certain differential

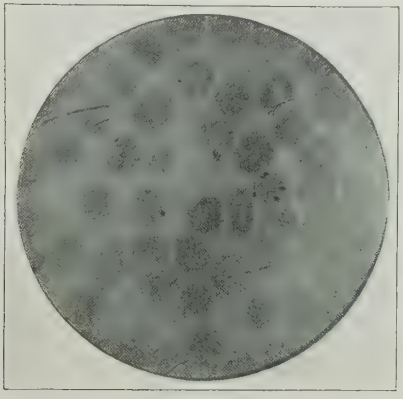

Fig. 9.—Plasmodium falciparum (Tertian estivo-autumnal plasmodium). Multiple invasion with the estivo-autumnal parasite.

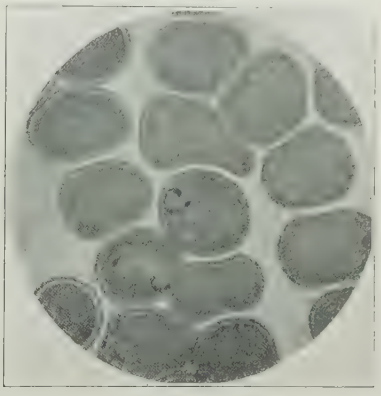

Fig. 10.—Plasmodium falciparum (Tertian estivo-autumnal plasmodium). Young ring forms. (After Craig.)

points in its morphology. It is considerably smaller than either of the parasites previously described, and as the schizont develops the difference in morphology allows of no mistake. The infected cell appears smaller and is of a green color. In the young forms of the parasite the protoplasmic ring is broader at one point of its periphery than the remainder, giving to it a characteristic "signet-ring" appearance; it is a very refractive organism and possesses but slight ameboid motion. Pigment is formed while the parasite is in the ring form, usually appearing, in the broad part of the protoplasmic ring, at about the end of eighteen hours; the granules are of a reddish color and are motile but not so actively as in the benign tertian parasite. The organ-

ism loses its ring form at about the end of twenty hours, at which time about half of the cell is occupied; ameboid motion always sluggish becomes then even more so. As the presegmenting stage is reached the parasite occupies about one third of the cell, the pigment collects in a single mass in or close to the center of the organism, the usual radial segmentation takes place, as in the forms already described, resulting in the formation of from ten to eighteen merozoites, which are arranged very irregularly and not in the definite circular arrangement described in the tertian and quartan types. (Fig. 11.) The merozoites continue the schizognic cycle in the same manner in all types of malaria. Sporulation of this

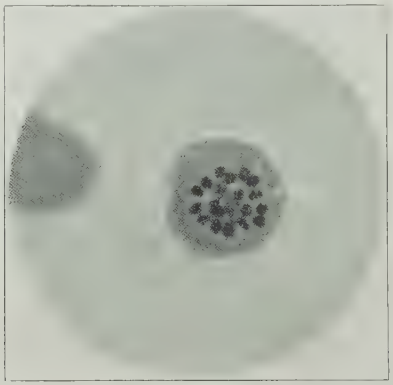

Fig. 11.—Plasmodium falciparum (Tertian estivo-autumnal plasmodium). Segmenting form of the parasite. (After Craig.)

parasite in the peripheral blood is rarer than in the benign tertian, being seldom seen there, taking place almost entirely in the visceral circulation.

The changes occurring in the red corpuscles will be discussed with those taking place in the quotidian estivo-autumnal type, with which they are common.

Quotidian Estivo-Autumnal Malaria (Plasmodium Falciparum Quotidianum).—This species of the malarial parasite completes its cycle in twenty-four hours. While it is claimed that it is rather confined in its area of distribution, the author has encountered it in Florida, and is rather of the opinion that it is of greater frequency in the Southern states than is generally believed.

Like other varieties of the plasmodia, it is first seen in the red

corpuscle as a small, round, hyaline ring and early assumes great activity, rapidly increasing in size, the young schizont occupying about a sixth of the infected cell. At first an indistinct body, it soon becomes very refractive, and the outline of the organism is well defined. The infected cell early becomes smaller than the surrounding ones, is often crenated, and appears to be shrunken. The signet-ring appearance, just described as characteristic of the malignant tertian, is not seen in this variety, the young plasmodia are considerably smaller, and ameboid motion is much more marked. It will be remembered that the pigment develops in the malignant tertian while the parasite is still in the ring form; in this type of infection pigment is not observed until the ring form is lost. The granules are very scanty, there seldom being but two or three and more often but a single one; they are entirely devoid of motion, thus differentiating this parasite from all other pigment forms, are of a dark brown or sometimes black color, generally situated near the center, but occasionally on the side of the organism. The infected cells have been termed "brassy corpuscles," owing to the peculiar color they assume in this infection.

Sporulation seldom takes place in the peripheral blood, but may be observed in blood specimens taken by splenic puncture, or, in post-mortems, in blood from the deep tissues. It takes place at the end of twenty-four hours and, following radial striation, the presporulating plasmodia is composed of six to eight round bodies, the merozoites. The quotidian are smaller than the malignant tertian merozoites, and the entire presporulating body occupies, as a rule, not more than a quarter of the infected cell.

The red corpuscles when invaded by either of the estivo-autumnal parasites become very much smaller. It will be remembered that in the benign tertian infections the cell is very much enlarged, of irregular shape, characterized by the presence of Schuffner's dots, and becomes pale; that in the quartan infections it becomes smaller, assumes a green appearance, and may be retracted. The decrease in the size of the cell invaded by the estivo-autumnal parasite is very much more marked, and the infected corpuscle becomes a darker green. In the quotidian variety the cells are more wrinkled or shrunken and more crenated than in the malignant tertian, while the brassy corpuscles seen in both types of estivo-autumnal infections are especially common in the quotidian. Schuffner's dots are not present in either of these infections.

While the changes occurring in the red corpuscles in the benign tertian are so characteristic as to allow of no error, and would be sufficient in themselves to make a diagnosis, the changes observed in the quartan and the estivo-autumnal infections are much less marked, and unless one is perfectly familiar with the blood picture of these malarial infections, errors are easily made. In both the quartan and the estivo-autumnal infections there is a decrease in the size of the corpuscle, the extent of which depends on the infecting organism.

The tabulation of differential characteristics of the various parasites, together with the changes taking place in the corpuscles, shown in Table I, will be of assistance in arriving at the determination of a species.

STAINING REACTIONS OF THE PLASMODIA.

The staining reactions of the various species of malarial plasmodia, as seen in the peripheral blood of man, are common to all species. While any of the stains described later may be used, the author has used with universal success Wright's modification of the Leishman stain. The technic of the application of this staining fluid, together with that of other staining methods, will be found in another chapter. With familiarity, which is easily acquired, in the use of this stain, the resulting picture renders a laboratory diagnosis of the malarial infections an easy matter.

Tertian Parasite.—For reasons already given, the tertian parasite is the one of choice for the beginner to familiarize himself with. All of the forms of schizogony may be seen in the peripheral blood, although sporulation occurs more generally in the deeper tissues. When stained the young parasite, a ring form, is seen to consist of a mass of protoplasm, staining an intense blue, containing a vesicular nucleus which holds within it a goodly amount of chromatin, staining an intense red, and being the only portion of the nucleus that takes a stain. The blue-stained protoplasm surrounds this unstained area, and is thinnest at that portion of its periphery where the chromatin appears, in fact, may be almost invisible at this portion of the periphery, careful focusing being necessary to detect it. The unstained area representing the vesicular nucleus is spherical or oval and is in contact with a larger area, unstained or lightly stained about the same as a red corpuscle, which is of a

TABLE I.

	Tertian.	Quartan.	E.-A. Quotid.	E.-A. Tertian.
Human cycle	48 hours.	72 hours.	24 hours.	48 hours.
Refraction	Low.	High.	High.	Very high.
Changes seen in red corpuscles	Considerably enlarged, takes on irregular shapes as parasite enlarges, becomes pale in color, Schuffner's dots present.	Normal size or smaller, often retracted about parasite, dark-green color, absence of Schuffner's dots.	Much smaller than normal, wrinkled and crenated, a green color, darker than in the quartan infection, most cells having brassy appearance.	Much smaller than normal, wrinkled and crenated, neither of these changes as marked as in E.-A. Quotidian. Brassy corpuscles present but not so frequent as in E.-A. Quotidian.
Pigment	Large in amount, very active, fine granules of a reddish-brown color, irregularly scattered through the protoplasm.	Not in such quantity, of slight motility, very coarse, dark brown, distributed round periphery.	Very few granules, nonmotile, almost black, situated usually near the center of organism.	Few minute granules, very active, reddish color, may be seen in young ring forms.
Size of adult parasite...	As large and frequently larger than red corpuscle.	Equal size or slightly smaller than a normal red corpuscle.	From one-quarter to a third the size of a normal red corpuscle.	From one-half to three-quarters the size of a normal red corpuscle.
Motility	Very active.	Sluggish.	Sluggish.	Active.
Appearance of presporulating form	Two irregular circular rows of spores.	One even and regular circular row of spores.	Arrangement of spores very irregular.	Unevenly distributed throughout the cell.
Site of sporulation.....	Occasionally in peripheral circulation, principally in that of the viscera.	Very frequently in peripheral circulation, more so than any of the other types, also in the circulation of the viscera.	Visceral circulation, rarely in the peripheral circulation.	Visceral circulation, very rarely in the peripheral circulation.
Number of merozoites contained in sporulating body	12 to 24.	6 to 12.	6 to 8.	10 to 18.
Shape of gametes seen in the human blood.....	Spherical.	Spherical or circular.	Crescentic.	Crescentic.

light pink or straw color. This larger area represents a vacuole that has formed alongside the nucleus.

As the parasite loses its ring form, the activity of the pigment, as it forms in the young schizont, causes the organism to take on various fantastic shapes, which are very prettily shown in the stained specimen, many varieties of these shapes being seen in a single specimen. As pigmented forms develop, the pigment is distributed throughout the protoplasm of the organism, the vesicular portion of the nucleus being gradually lost sight of. With the further growth of the parasite the chromatin separates into small granules, becoming irregularly situated throughout the protoplasm, and does not take as intense a stain as formerly. As the presporulation stage is reached, the protoplasm, studded with pigment granules stained a greenish-brown, increases in amount and takes a heavy stain; the chromatin is seen to be gathered in clumps and also stains intensely. When segmentation has taken place, and the merozoites are formed, the chromatin granules are seen in still larger clumps, staining a dark red, each surrounded by an unstained area, these, being surrounded by small bands of protoplasm, staining blue; the pigment, as a rule, collects in a single mass in some portion of the protoplasm. The merozoites, having gained access to red cells, appear under the Wright stain as a small mass of protoplasm staining blue, enclosing an unstained oval area which has within it a small dot of chromatin staining a bright red.

The staining reactions of this parasite may be summed up as follows: With the young ring forms is seen a small mass of protoplasm, thinner at a certain portion of its periphery, staining a deep blue; at that portion of the blue-stained protoplasm presenting the narrowest surface is seen a small particle of chromatin, which takes on a deep-red or sometimes a violet color, and surrounding this small mass is an unstained area, or one lightly stained as the corpuscle, this being a vacuole that has developed around the nucleus. As the parasite grows, the protoplasm increases in size, takes on irregular shapes, and contains more or less pigment scattered through it, which stains a greenish-brown. As sporulation advances, the picture is one that would be looked for with a knowledge of the changes taking place in the unstained specimen; the chromatin is seen to become divided, finally forming into small clumps, each of which later are seen as minute dots in the individual merozoites. The merozoite after sporulation takes

on the same staining reactions observed in the original young forms.

Quartan Parasite.—The staining reactions of the quartan parasite are very much the same as observed in the tertian variety just described, but there are certain differences that may be seen by close observation. The protoplasm by comparison takes a more intense stain from the methylene blue, and the chromatin, generally located in the center of the young schizont, takes a dark-red stain, while the young forms, which like the tertian are also ring-shaped, are slightly larger than those of the tertian variety. Characteristic of this form of malarial infection are the "band forms" of protoplasm, staining a dark blue and occupying the diameter

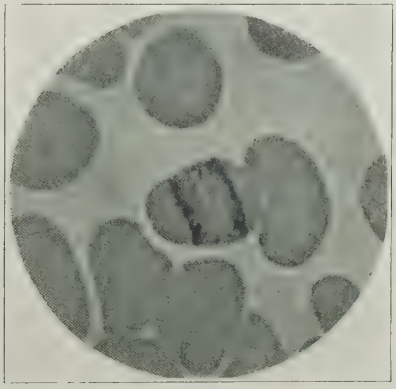

Fig. 12.—Plasmodium Malariæ (Quartan plasmodium). Band form of the parasite. (After Craig.)

of the red cell, or nearly so. (Fig. 12.) They inclose a chromatin mass which stains in the usual red manner.

The fantastic irregular shapes assumed by the tertian parasite are not seen in quartan infections, this parasite assuming a circular contour. The pigment, not abundant, is not distributed throughout the protoplasm as in the tertian but tends to collect on the periphery of the organism.

Estivo-Autumnal Parasites.—The staining reactions of the estivo-autumnal parasites present no especially significant characteristics. The ring forms present a very thin band of protoplasm, and the chromatin, instead of being contained within the periphery of the protoplasm, as it is in the tertian and quartan infections, often projects outside of the periphery. In the malignant tertian organ-

ism pigment will be observed in the young ring forms contained in that portion of the protoplasm where it is the broadest. The small size of the ring form, the protoplasm being a thin band, situated in a corpuscle smaller than those not infected, and often presenting a wrinkled or crenated appearance, will be sufficient to differentiate these organisms from either the benign tertian or the quartan.

DESCRIPTION OF GAMETES AND STAINING QUALITIES.

The sexual forms of the malarial plasmodia, destined for evolution in the mosquito, have already been referred to as macrogametes (female), and microgametocytes (male), and the author has already described the circumstances under which the latter become flagellate bodies, later giving off flagella, the fully formed microgametes.

The gametes of the benign tertian are difficult to recognize in the fresh blood until they reach maturity. Unlike the schizont they retain a circular shape, being from two-thirds to twice the size of a red corpuscle, the macrogamete being slightly larger than the microgametocyte.

The unstained macrogamete appears as a circular protoplasmic body containing much pigment, which is situated near the periphery of the organism in a wreath-like manner. It is non-motile, this being an important point in differentiating the female from the male, in which the pigment is actively motile.

When stained by Wright's method the protoplasm takes an intense blue; the chromatin, less in amount than in the fully developed schizont, and situated near the periphery of the organism, stains, as in the schizont, a bright red. The pigment, already described as circling close to the periphery, is rod-like, massed irregularly, and very dark.

The microgametocyte of tertian malaria is a smaller body than the female, being about the size of a red corpuscle or slightly larger. When maturity is reached it is free in the blood-plasma and is made up of protoplasm containing a large amount of pigment, and at first only slightly motile. Unlike the pigment arrangement in the macrogamete, which appears in a wreath-like manner near the periphery, in this organism it is irregularly distributed within the protoplasm. Under the conditions previously described, the pigment will be observed to increase in activity, collecting toward the

center, this being followed by decreased motility; and as this activity decreases, long thin filaments, numbering from two to six, the young microgametes, destined to fertilize the macrogametes, are seen to protrude from the periphery of the organism. They are extremely active and may be seen to lash about, finally becoming free from the parent body, coming in contact with the female, which they penetrate and fertilize. This process normally occurs within the body of the mosquito, and sporogony is thus established.

The staining reactions of the microgametocyte are similar to those seen in the female form. As already stated, the pigment is more abundant than in the macrogamete, being unevenly distributed through the protoplasm, and staining a light green, the protoplasm a light blue; while the chromatin, greater in amount, stains an intense red, which in the fully developed organism is divided into several masses which occupy a position near the periphery of the body, and as the flagella develop, these divided chromatin masses become situated in the filaments, which later develop into fully formed microgametes. In these forms the protoplasm stains the usual blue, the chromatin taking on an intense red, increasing in amount after leaving the parent body, which undergoes degeneration.

In the younger forms the gametes of the benign tertian may be differentiated from the young schizont, when stained, by the position of the red-stained chromatin, which occupies the center of the ring of blue-stained protoplasm. The nutrient vacuole, described in the young schizont, is absent in the gamete-trophozoite.

The differences between the gametes of quartan malaria and those of the benign tertian are so minute that a separate description of them is not necessary. In the young intracorpuscular forms, the smaller bodies together with absence of the increased size of the corpuscle will serve to differentiate them from the young tertian gamete. The nutritive vacuole is absent, but loses its significance as it is also absent in the young quartan schizont early in its development.

The staining reactions of the fully developed forms are similar to those of the tertian variety. The macrogametes are larger than in the benign tertian, and contain less chromatin which remains as an intact mass. The microgametocytes are considerably smaller than the tertian, and the pigment contained in them is

much coarser. The fully developed microgamete has nothing to differentiate it from that of the tertian male gamete.

What has been said in regard to the schizonts of the benign tertian infection, as being suitable for the novice to work with, is equally true of the sexual forms of the estivo-autumnal infections. The peculiar crescentic formations assumed by these bodies make their identification an easy matter, and once they are seen and recognized, it is impossible to mistake them or to fail to properly recognize them. When once formed in the blood they are the most persistent and the hardest forms to eradicate, but they are not present in all cases; in fact, the majority of cases fail to reveal the presence of sexual forms. Craig is of the opinion that a careful examination of the peripheral blood will show crescents in 50 per cent of the infections, but has been unable to demonstrate them in but a little over 33 per cent of his examinations; but he thinks that a careful examination of smears from the spleen or bone marrow will greatly increase their percentage. It is especially in these infections, requiring a long and persistent examination of the peripheral blood for the detection of the sexual forms, this detection being such an important factor in the prophylaxis of the disease, that the application of the thick-film method in the examination of blood, originally advocated by Ross, is of especial value; this method will be dwelt on at length in another chapter. The morphology of the sexual forms in both types of estivo-au-

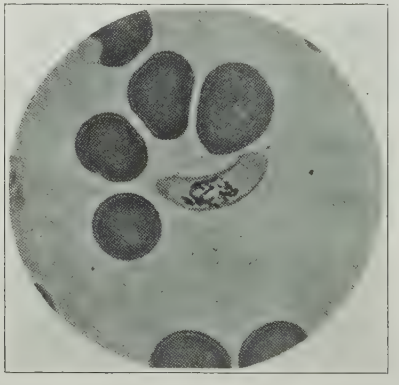

Fig. 13.—Plasmodium falciparum (Tertian estivo-autumnal plasmodium). Female crescent. Macrogamete. (After Craig.)

tumnal infection are very similar, the only differences being in the general contour and size, and will be considered together. Both forms, male and female, assume crescentic shapes and develop within the red corpuscle.

The macrogamete (Fig. 13) is characterized by its long slim crescentic form; it measures in length from one and a half to two times the diameter of a normal red corpuscle. Pigment collects in the center of the organism, is non-motile, and is usually seen in an irregular mass in this position, but may assume a wreath-like arrangement slightly removed from the center. After becoming extracorpuscular, the macrogamete is of an ovoid shape, later tak-

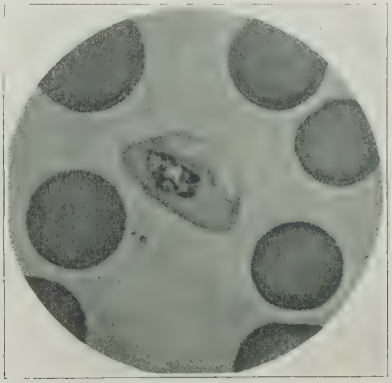

Fig. 14—Plasmodium falciparum (Tertian estivo-autumnal plasmodium). Male crescent. Microgametocyte.—(After Craig.)

ing on the form of a crescent. There are but slight differences in the macrogamete of an estivo-autumnal quotidian and an estivo-autumnal tertian. The former is slightly smaller, and the pigment contained within the female gamete is in the form of fine granules, while in the tertian it is rod-like, and in a larger amount.

The protoplasm of the macrogamete stains a light blue still lighter in the center, which contains the chromatin, stained red. The pigment, as previously described as assuming a wreath-like appearance, surrounds the chromatin, and is stained a dark-green color. The corpuscle containing the organism is generally barely discernible, close inspection showing it in the form of a ribbon-like band closely

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adherent to the external surface of the organism and stained a yellowish-pink or straw color.

The microgametocyte (Fig. 14) of the estivo-autumnal infections is differentiated from the female by the bean-like shape of the organism. It will be recalled that the macrogamete is a long slender crescentic form; the male or microgametocyte is shorter, thicker, and of a bean-like shape. The pigment is finer, and instead of being collected in the center in a mass or wreathed near the center as in the macrogamete, is distributed throughout the protoplasm of the body, or may be collected at the extremities. When transferred to the body of the mosquito it throws out flagella, common to all microgametocytes, which penetrate the females and fertilizes them.

The staining of the microgametocyte is similar to that of the female form, except that the stains are taken more deeply, the protoplasm staining a deeper blue, while the chromatin, distributed throughout it, takes a light red or pink, and the pigment, situated at either end of the crescent, an indistinct greenish-brown. The appearance of the remaining corpuscle is similar to that containing a macrogamete.

The microgametes are the flagella thrown out by the microgametocyte on reaching the body of the mosquito. As they are being formed, the microgametocyte loses its crescentic or bean-like shape, and assumes a more circular form, the pigment becomes actively motile, and filaments are thrown out, these numbering from one to three in number, occasionally four, and when disengaged from the parent body, constitute the fully developed microgametes. The general description of the microgamete of the benign tertian applies to the microgamete of all species, it being impossible to differentiate between those of any of the malarial infections, and their staining qualities are also exactly similar.

The young gametes when stained by Wright's stain may be differentiated from the young schizonts by the following characteristics: the chromatin in the gamete is observed in the center of the organism instead of on the periphery, as seen in the schizont; pigment is in larger amount, is not so motile as in the schizont; and the protoplasm stains a more intense blue.

CHAPTER III.

ETIOLOGY—THE MALARIA-CARRYING MOSQUITOES.

In discussing the etiology of malaria with the laity, the general practitioner will often find the erroneous opinion held that any and all mosquitoes may transmit the disease. While a great number of species have been mentioned as possible carriers by various writers, the list of which I will not burden the reader with, the following are those that have been actually incriminated as malaria carriers, this list being one compiled by Craig:

GENUS, *Anopheles*. *A. maculipennis*, Meig; *A. bifurcatus*, Linn; *A. algeriensis*, Theo.; *A. jasoensis*, Tsuzuki; *A. formosaensis*, Donne; *A. cohaesus*, Donne; *A. quadrimaculatus*, Say; *A. albipes*, Giles; *A. vagus; A. vincenti; A. martini; A. pursati*. 12 species.

GENUS, *Myzomyia*. *M. listoni*, Liston; *M. funesta*, Giles; *M. turkhudii*, Liston; *M. culicifacies*, Giles; *M. nili*, Theo.; *M. hispaniola*, Theo.; *M. ludlowii*, Theo.; *M. lutzii*, Theo. 8 species.

GENUS, *Stethomyia*. *S. nimba*, Theo. 1 species.

GENUS, *Pyretophorus*. *P. costalis*, Loew; *chaudoyei*, Theo.; *P. ardensis*, Theo.; *P. superpictus*, Grassi; *P. jeyporensis*, Theo. 5 species.

GENUS, *Arribalzagia*. *A. maculipes*, Theo. 1 species.

GENUS, *Myzorhynchus*. *M. sinensis*, Wied; *M. barbirostris*, Van der Wulp; *M. pseudopictus*, Grassi; *M. paludis*, Theo.; *M. mauritianus*, Grandpre and Charmoy; *M. coustanii*, Lav. 6 species.

GENUS, *Nyssorhynchus*. *N. fuliginosus*, Giles; *N. stephensii*, Liston; *N. maculipalpis*, Giles; *N. theobaldii*, Giles. 4 species.

GENUS, *Cellia*. *C. argyrotarsis*, Robineau-Desvoidy; *C. pharoensis*, Theo.; *C. albimanus*, Wied. 3 species.

He gives the geographical distribution of these species as follows:

West Indies: *Cellia argyrotarsis, Cellia albimanus.*

Canada: *Anopheles maculipennis.*

United States: *Anopheles maculipennis, Anopheles quadrimaculatus, Cellia argyrotarsis.*

Central and South America: *Anopheles albipes, Arribalzagia maculipes, Pyretophorus lutzii, Cellia argyrotarsis, Myzomyia lutzii, Cellia albimanus.*

Europe: *Anopheles maculipennis, Anopheles bifurcatus, Myzorhynchus pseudopictus, Pyretophorus superpictus, Myzomyia hispaniola.*

Asia: India—*Myzomyia culicifactes, Myzomyia listonii, Myzomyia turkhudii, Pyretophorus jeyporensis, Myzorhynchus barbirostris, Myzorhynchus*

sinensis, Nyssorhynchus theobaldi, Nyssorhynchus stephensii, Nyssorhynchus fuliginosus, Nyssorhynchus maculipalpis.

Japan: *Anopheles jesoensis, Anopheles formosæensis, Anopheles cohæsus.*

Africa: *Myzomyia funesta, Myzomyia nili, Pyretophorus costalis, Pyretophorus ardensis, Pyretophorus chaudoyei, Myzorhynchus barbirostris, Myzorhynchus mauritianus, Myzorhynchus paludis, Cellia pharœnsis.*

Madagascar: *Myzorhynchus coustanii.*

Mauritius: *Myzorhynchus mauritianus.*

The Philippine Islands: The following malarial mosquitoes have been found in the Philippine Islands by Ludlow, Whitmore, Banks, and the writer: *Myzomyia funesta, Myzomyia ludlowii, Myzorhynchus barbirostris, Myzorhynchus sinensis, Nyssorhynchus fuliginosus.* Further observation will undoubtedly demonstrate that other species occur in these islands.[1]

HABITS OF THE ANOPHELINES.

A general knowledge of the habits of the *Anophelines* is essential. It may be generally stated that they are night feeders, and that those persons who keep themselves protected from sundown to sunrise will escape infection. This was markedly demonstrated by Doctor Sambon and his associates in the Roman Campagna, and yet it is probable that under certain conditions, and in certain climates, there are exceptions to this rule. Craig states that, in the Philippine Islands, he has frequently observed the *Myzomyia funesta* feeding in the early morning and even at noon, and Le Prince, Chief Sanitary Inspector of the Isthmian Commission, in a study of mosquitoes seen in Panama, writes as follows:

The *albimanus* generally leaves the dwelling during the daytime. It is present and bites more readily after dark. However, it will bite voluntarily at any hour of the daytime, but does so mostly indoors or out of the direct rays of the sun. If *Anophelines* are resting in vegetation near houses, and such vegetation is disturbed, burned, or removed, they will often seek shelter in the nearest buildings. This habit is common to other mosquitoes in the tropics. In a badly infested vicinity such a removal of the natural resting place will send scores of mosquitoes into the nearby houses. It is not yet known whether the malaria-conveying *Anophelines*, when numerous in a shaded area containing tall grass, brush, and trees, will bite malarial persons resting in such places in the daytime, and remain in the vicinity long enough to transmit malaria to other persons that may come to rest, or sleep, in the same place in the daytime during the following weeks. It would seem as though this does take place, and if so, it may have an important bearing on the status of malaria in the Canal Zone.

[1] The above list does not include the *A. Crucians*, the most common carrier in Florida (Byrd) and Louisiana (Mitchell), and probably other southern states where mosquitoes have not been very closely studied.

In even the temperate climates it is a common occurrence to see *Anophelines* flying around dark corners of rooms and in closets, during the daytime, and they will under some circumstances feed, but their doing so must be an unusual occurrence, or those observing faithfully the sanitary laws for the prevention of malarial infec-

Fig. 15.—Resting position of Anopheles maculipennis, Meigen; enlarged. (After Howard.)

tion would not remain as uniformly free from the disease as they do.

The consensus of opinion is that in the more temperate climates day-feeding is very unusual, that they may feed at all times in certain tropical countries, but that in even these they are naturally nocturnal feeders.

The resting position of the *Anophelines* is characteristic (Fig. 15),

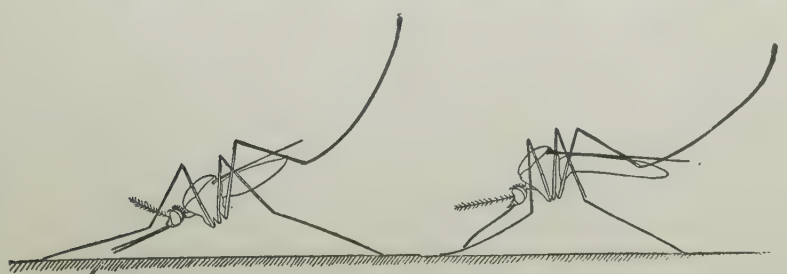

Fig. 16.—Resting position of Anopheles and Culex. (After Howard; from sketch by Waterhouse.)

and of itself is sufficient to differentiate them from other groups. Its body, instead of assuming a parallel position with the resting surface, is seen to be at an angle of 45° to it. This is caused by the proboscis, head, thorax, and abdomen forming a straight line;

while in the *Culex,* the proboscis, head, and thorax form an angle with the abdomen (Fig. 16).

There has been a great difference of opinion expressed as to the distance that the *Anophelines* will fly. The question is an important one when considering the feasibility, in a given district, of destroying the local breeding places, thus maintaining a sanitary

Fig. 17.—Anopheles argyrotarsis, Desvoidy; adult female; enlarged. (After Howard.)

malaria area. While such destruction will always be followed by results, it is obvious that the same success will not attend the movement, if there are outside this area breeding places from which the mosquitoes will migrate. Craig states, from personal observation in the Philippine Islands, that he is satisfied that *Anophelines* will fly from two to two and a half miles in search of food. Observations recently carried on by Le Prince in the Canal Zone,

Panama, show that certain anophelines will fly long distances, and he has captured marked specimens 6,000 feet from the point of their liberation, while several specimens stained near their breeding places were found in the same localities two weeks later. It has been stated that the insect will seek, for the deposit of her eggs, the same breeding place from which she originated, and that this choice of breeding place will be sought for several succeeding generations.

Mosquitoes are capable of hibernation in both the larvæ or winged state. Only the female winged insect is capable of doing this, the adult males dying early in the cold months.

Fig. 18.—Female of Anopheles punctipennis, Say; enlarged. (After Howard.)

GENERAL DESCRIPTION OF THE ANOPHELINES.

A lengthy description of mosquitoes and their biology, while of interest to the zoölogist, is not of practical value to the general practitioner, and for this reason we shall not go extensively into details, but will pass the subject with a few statements concerning

the chief points of interest in the anatomy of the *Anophelines* as differentiating them from other mosquitoes. The chief points of anatomical interest are the proboscis, the palpi, the antennæ, and the salivary glands.

The proboscis is a hollow tube representing the insect's mouth, which allows her to draw the blood into her stomach during the biting process. The palpi, two in number, are situated on each side of the proboscis, and in the female are of equal length, or nearly so, to the proboscis, this being an important differential point in determining an *Anopheline* from the *Culex,* in which they are very

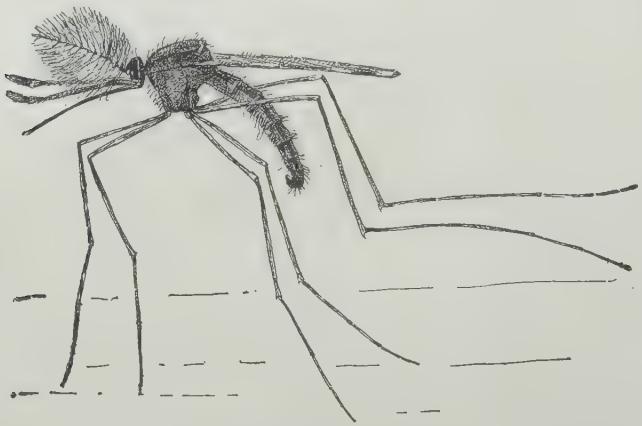

Fig. 19.—Male of Anopheles punctipennis, Say; from side; enlarged. (After Howard.)

short. The antennæ arise from a point on the head close to the palpi, and in the female, the only one capable of carrying the infection, can be differentiated from those of the harmless male by the difference in their appearance, those of the female having a few straight hairs of great relative length, while on those of the male insect the growth of hair is much heavier and broadens into plumes, making a pretty and definite picture under a low-power objective, and also discernible to the naked eye. The salivary glands are of especial interest, as it is in them that the sporozoites are lodged with which the mosquito inoculates man with malaria. These, two in number, are connected with the proboscis, at the base of which are situated voluntary muscles that allow the insect to inject her saliva into man in the biting process.

DEVELOPMENT OF THE MALARIAL PLASMODIA IN THE MOSQUITO.

This has been briefly referred to in the preceding chapter. The various changes of the parasite in its evolution within the body of the mosquito have been carefully observed by many investigators, and the following detailed description is taken verbatim from a recent work by Craig, who has kindly given his consent. The observations, he states, are derived from the studies of Schaudinn,

Fig. 20.—Anopheles crucians, Wiedemann; adult female; enlarged. The most common species found in the southern states. (After Howard.)

Grassi, Bastianelli, Bignami, together with his own, and is probably the most complete description that has been written:

Previous to the formation of the microgametes, the microgametocytes undergo certain changes which are of interest. The nucleus gives off a large amount of chromatin, which becomes arranged about the periphery of the organism, and which enters into the formation of the thread-like microgametes. It would appear that this chromatin is taken up by the microgametes just before the latter emerge from the body of the microgametocyte, for in stained specimens it is but seldom that any chromatin is observed in the residual body immediately after the appearance of the microgametes.

The only change observed in the macrogamete prior to fertilization concerns the nucleus, a portion of the substance of which is claimed by Schaudinn to be eliminated.

When fertilization occurs, the microgamete penetrating the macrogamete, the chromatin of the former constitutes a pronucleus which fuses with the female pronucleus of the macrogamete, and a fertilization spindle is thus formed, which is often very well defined in properly prepared specimens. The organism resulting from the union of the micro- and macrogamete, or the zygote, does not encyst, but develops into an elongated vermicule or oökinete.

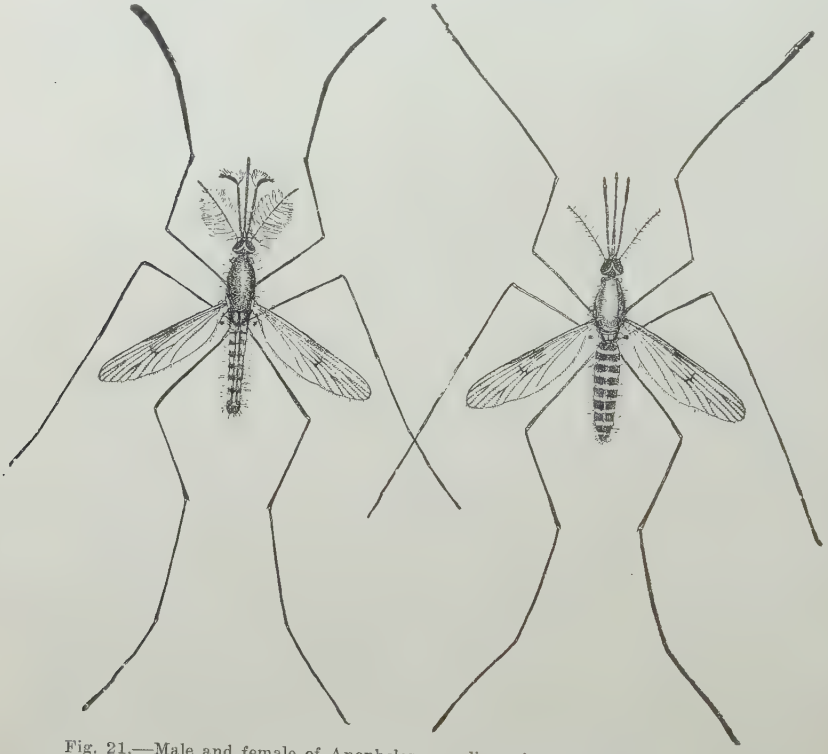

Fig. 21.—Male and female of Anopheles maculipennis, Meigen. (After Howard.)

This body is somewhat oval in shape, the anterior extremity being very narrow and pointed, while the posterior extremity is broad and rounded in appearance. The nucleus is situated a little posterior to the middle of the body and is composed very largely of chromatin, which takes a deep-red stain with Wright's method of staining. The pigment is collected in a loosely arranged mass near the posterior extremity and later in the development of the oökinete may be extruded or may be retained until the formation of the sporozoites, when it is liberated together with a portion of residual protoplasm. The movements of the oökinete are very active, consisting of contractions of the

body and of a rapid progressive motion, gliding in character, no satisfactory explanation of which has as yet been given. Schewiakoff believes that the gliding progressive motion is due to the secretion and extrusion of a gelatinous thread which pushes the organism forward as it is formed, while Crawley thinks that the motion is due to wave-like contractions of the protoplasm. However the motion is produced, it enables the oökinete to force its way through the epithelial lining of the mosquito's stomach and reach that portion of the stomach wall immediately beneath the epithelial lining, where it rests and the oöcyst is formed. When it reaches this locality the oökinete becomes spherical in shape and secretes a delicate covering membrane, continuing to grow until it projects from the stomach wall toward the body cavity of the insect.

The nucleus divides, and each daughter-nucleus is surrounded by a portion of protoplasm, forming the sporoblasts; the sporozoites are developed within the sporoblasts by the repeated division of the nucleus of each sporoblast, the small nuclei thus produced accumulating upon the surface of the sporoblast and forming delicate protoplasmic prolongations, each consisting of a little protoplasm and a clump of chromatin, eventually forming the sporozoites. When development is complete, the cyst is filled with a multitude of sporozoites together with some residual protoplasm, and in many instances considerable pigment. When the cyst ruptures, the sporozoites are liberated in the body cavity of the insect and are carried by the blood to the salivary glands, from which they pass down the proboscis to the blood of man when the mosquito bites. The sporozoites are actively motile, spindle-shaped, and measure about 14 microns in length.

The time consumed in sporogony has been variously estimated at from 10 to 14 days, the average being 10 to 12 days. It varies, in all probability, with each species of plasmodium, but never exceeds 14 days.

The fertilization of the macrogamete by the microgamete, first observed in human malaria by MacCallum, has been observed by Koch, in Africa, and by Ashburn and myself, in the Philippine Islands, in blood from malarial cases removed for some time from the body.

To those who are interested in tracing the development of the malarial plasmodia within the mosquito, the following description, arranged in periods of time may prove useful:

First and Second Days After Ingestion of Malarial Blood.—The fusiform and spindle-shaped oökinetes penetrate the epithelial lining of the insect's stomach and reach the muscular layer, where they encyst and form the oöcyst. In stained specimens the oökinete presents at or near the center a deep-red chromatin mass, representing the nucleus, the chromatin being in the form of short, very delicate threads or granules. The pigment is collected in a dense clump at the posterior end or is distributed throughout the protoplasm; the protoplasm contains numerous vacuoles and stains a light-blue color. The oöcyst at the end of two days is about the size of a red blood corpuscle, contains considerable pigment distributed throughout the protoplasm, and the chromatin is found in small granules or in minute irregular masses, collected toward the center of the organism.

Third and Fourth Days.—During the third and fourth days the oöcyst

increases to twice its original size, and develops a well-marked cyst wall. The pigment is not increased in amount, and is collected in small masses; the protoplasm is vacuolated, and the chromatin is distributed throughout it in fine granules or delicate threads.

Fifth and Sixth Days.—At the end of the sixth day the cyst has increased very greatly in size, measuring from 35 to 75 microns in diameter, and projects from the wall of the stomach outward toward the body cavity of the insect. The protoplasm appears granular, and large, very refractive spherical bodies may be distinguished within it, the sporoblasts. The pigment has not increased in amount and, owing to the great increase in size of the organism, appears to have greatly diminished; in some instances the cyst, at this stage, is devoid of pigment. The chromatin is collected in the sporoblasts and stains red, while the protoplasm stains a very pale blue.

Seventh to Eighth Days.—Under favorable circumstances, and in some species of Anophelina, the cysts have attained their full growth in eight days. At this time a well-marked double-outlined membrane surrounds them, which is perfectly smooth in contour; the sporoblasts form common centers from which radiate multitudes of delicate, elongated, spindle-shaped, or thread-like bodies, the sporozoites. The sporozoites appear to originate from the outer layers of the sporoblasts, each sporozoite being attached by its inner extremity to a small portion of the residual protoplasm of the sporoblast. When isolated and stained each sporozoite measures from 12 to 14 microns in length, and contains one or more masses of chromatin imbedded in the light-blue protoplasm. When fully developed the sporozoites become detached from the sporoblasts, and the cyst is then observed to be filled with multitudes of these delicate filamentous organisms.

The above description applies to the tertian estivo-autumnal plasmodium, but practically the same appearances are observed in the mosquito cycle of the benign tertian and quartan plasmodia. It should be remembered that in any one insect all of the plasmodia are not in the same stage of development at the same time, some being more advanced than others, but the periods as given are true for the vast majority of estivo-autumnal plasmodia, in most species of Anophelina. Unless the temperature be suitable, the development may be delayed to 12 or even 14 days, and in *Myzomyia funesta*, a very common malaria carrier, the cycle of development at 80° F. always takes 12 days.

After the sporozoites are liberated into the body cavity of the insect by the rupture of the cyst wall, they may be observed in fluid from any portion of the body of the insect, and if the cells of the salivary glands be examined numerous sporozoites will be seen within them, as well as within the salivary ducts.

CHAPTER IV.

ETIOLOGY—OTHER FACTORS.

There are many conditions that in an indirect manner favor the endemicity or epidemicity of the disease, and while two factors, certain mosquitoes and malaria-infected man, are necessary for the production of it, it is well to bear in mind all those conditions that, in an indirect manner, favor the spread and perpetuation of the infection.

PREDISPOSING FACTORS.

Climate.—Heat and moisture being necessary for the breeding of mosquitoes, it stands to reason that malarial infections will be more common in warm climates than in the temperate ones. Not only are malarial infections more common in tropical and subtropical climates, but the disease is more virulent in these countries. Malignant infections will seldom if ever be seen in the temperate regions, while the estivo-autumnal infections are often the preponderating ones in warm countries. The parasite will not develop in the mosquito where the mean temperature is below 60° F., and there are many species of mosquitoes in which the parasite will not develop except at a temperature much higher than even this, so that, in sections of a country where the autumn or winter temperature drops below this level, the mosquitoes that are infected become sterile and incapable of transmitting the disease, until a temperature of above 60° F. is maintained a sufficient time to allow the development of the sporozoites, after the mosquito becomes reinfected from some chronic gamete carrier. The body temperature of man is always at a sufficiently high point to allow the presence of the sexual forms of the parasite, so that, in these communities where weather conditions are such through the winter months as to interfere with the development of the parasite in the mosquito, and the early warm months find the mosquito, though present, sterile, the sexual forms with which the insect becomes reinfected when biting man not being removed; after a certain period, rep-

resenting the time necessary for the development of the sporozoites in the mosquito, together with the period of incubation required for the disease to become manifest in man, the disease reappears.

Deaderick states that Hirsch marks the northern boundary of malarial infections in the northern hemisphere as ranging from 45 to 65 degrees north latitude, "the line starts from 55 N. on the western side of North America, sinks to 45 on its eastern side, rises to 63 or 64 on the western sides of the old worlds (Sweden and Finland), and runs across Northern Asia in about the latitude of 55." All territory south of this line may be regarded as within the malarial zone, but there are many sections free from malarial infection, owing to the fact that the parasites are not present in the circulation of the inhabitants, and without that focus of infection, the mosquito is of course harmless.

Altitude.—As a general rule, it may be said that high altitudes are not conducive to malarial infections. Climatic conditions are partially responsible for this, together with the fact that all highlands naturally permit of drainage better than the lowlands, but there are, however, numerous exceptions to this rule, several observers reporting the infection at high altitudes. A person suffering from a latent form of the disease will frequently suffer a relapse following his removal to a high altitude, and we have at the present time no satisfactory explanation for this.

Rain.—Water being necessary for the creation of breeding places for the mosquito, it follows that rainy periods will later result in an exacerbation of the infection in a given community under favorable conditions for the transfer of the parasites from one host to the other. It is not infrequent, however, to have a heavy rainfall result in the destruction of already formed breeding places, by flushing them, clearing them of larvæ.

Season.—In most malarial countries the infection will gradually increase as the warm season advances, and the report of the Department of Sanitation of the Isthmian Canal Commission for 1911, illustrates how it increases with the warm months. (See Table II.)

This table shows a commencing rise in May, the maximum number of cases occurring in June and July, followed by a steady decline during the succeeding months.

The author has frequently observed that in the Southern states the infection often reaches the point of maximum intensity (nu-

TABLE II.

HOSPITAL CASES OF MALARIA AMONG EMPLOYEES.

Months.	Discharged.		Died.		Total cases.	Annual average per 1,000 of deaths.	Annual average per 1,000 of cases.	Number of employees.
	W.	C.	W.	C.				
January	180	157	1	1	339	0.51	86	47,348
February	217	166	1	...	384	.24	93	49,785
March	239	167	...	1	407	.25	102	47,935
April	190	138	1	...	329	.25	81	48,634
May	461	463	1	3	928	.99	230	48,496
June	756	981	4	4	1,745	1.98	432	48,519
July	747	1,226	4	4	1,981	2.01	497	47,801
August	396	506	3	2	907	1.21	219	49,710
September	322	339	3	...	664	.76	168	47,400
October	253	249	1	...	503	.24	121	49,812
November	199	210	4	1	414	1.19	99	50,420
December	191	193	1	1	386	.47	91	50,655
Total	4,151	4,795	24	17	8,987	.84	184	48,876

merically) late in the season, October, or even November. This is no doubt due to the slowly increasing number of gamete carriers resulting from indifferent treatment throughout the warm season, which results in a higher percentage of mosquitoes becoming infected as the season advances. It would be interesting to note the increasing percentage of infected mosquitoes as the season advances in a given community, where, owing to climatic conditions in the spring, they are sterile. As will be shown later, we cannot lay too much stress upon the significance of every additional gamete carrier in a community.

Occupation.—With our knowledge concerning the transmission of the disease, it stands to reason that occupation is a predisposing factor, those working at night, subjected to the bites of infected mosquitoes, necessarily being in greater danger of becoming infected than those not so exposed. It is also probably true that any occupation which necessitates the disturbance, during the daytime, of underbrush, or any material which may harbor the resting insect, will, in those sections where the mosquito feeds in the daytime, predispose to infection.

Race.—It has been claimed by some in the past that the dark-skinned races enjoy a greater degree of natural immunity to malarial infection than that possessed by the lighter-skinned races, but this view has been largely modified in more recent years. There is little question that a given number of negroes will not develop as many malarial infections as the same number of white

men under similar conditions, but this is no doubt due to a certain acquired immunity, attained in childhood. The mortality among negro children is appallingly high in some localities, and those that survive probably acquire a certain immunity—this will be discussed further in considering the immunity of the disease.

Sex and age.—Sex has no apparent influence on the disease, the same ratio of males and females exposed will become infected. Deaderick gives the following table of sex distribution in a few localities:

TABLE III.

	Males.	Females.
Stephensport	32	21
Italy	312	327
Alabama	585	451
Italy	311	236
Bulgaria	1,742	995
Italy	268	147
Greece	1,202	972
Baltimore	493	121
	4,945	3,270

While this table shows in the aggregate that more men than women were infected, it is probably due to the fact that, as a general rule, men are exposed to the infection to a greater degree than are women, and not to the fact that women possess any degree of immunity.

Children are more often attacked than adults, and in them the infection is generally more severe. They seem to be more susceptible to the poisons and do not possess the acquired immunity that older persons may obtain with long residence in malarial countries. Craig states that, from his observations in the Philippine Islands, while young children are more susceptible than older ones, in that country the adults suffer from the disease as much, or even more, than do the children.

Effect of Improper Diet.—As any condition that will reduce the resisting powers of the individual favors malarial, as well as other infections, it is but natural that improper food will in some instances precipitate attacks. It is not probable that this is an important predisposing factor in this country, but there are sections of the world where it is a very serious problem. Leslie, in speaking of conditions in India, states that:

> In the towns, in India as in other countries, there are numbers of people who lead a hand-to-mouth existence; ill-housed, ill-clad, and ill-fed, they pick up a precarious livelihood in the unskilled labor market. Such people have

unsuitable food at the best of times, and they have no savings, so that, when anything occurs to check the demand for such work as they can do, the scanty coarse food becomes scantier and coarser and they and those dependent on them offer little resistance to malarial infection and readily succumb to its effects. Analogous conditions, as pointed out by Christophers and Bentley, may be artificially produced in any area in which *Anopheles* breed, when large numbers of laborers are collected in it under bad hygienic conditions. The majority of such laborers are free from infection, but are highly susceptible to it, a few are infected, and all are dependent on their daily labor for their daily bread. Infection spreads and with it the inability to earn money to pay for sufficient food, privation added to malaria determines a severe attack, attacks are repeated, and here again the disease is a very fatal one.

Surgical Operations.—These will often wake up a latent infection, while any pathological condition that lowers the resistance of the individual will increase the likelihood of original infection; and it is a common occurrence to see a woman in the lying-in period develop symptoms which may arouse suspicions of sepsis, but which in reality are due to a recurrent malarial infection. An examination of the blood of such individuals is of paramount importance, for the purpose of demonstrating that the infection is of malarial origin and not due to puerperal sepsis.

Effect of Residence.—The period of time that will elapse before a newcomer in a malarial region will become infected is governed by many conditions. The prevalence of the disease, and the prophylactic measures taken by the individual necessarily enter largely into the matter. There are many sections of the world where malaria is endemic, but where individuals, observing proper precautions, have lived for years without ever becoming infected. Change of residence will often bring on an attack when the disease is latent, as mentioned in discussing the effect of altitude.

CONGENITAL MALARIA.

It has been a very much debated question as to whether the fetus in utero could become infected through the placenta, if the mother developed the disease during pregnancy. From a careful review of the literature together with personal observation, the author is of the opinion that the general evidence is arrayed against this theory, although it cannot be regarded as an absolutely settled question at this time. In all of the cases reported, in which it was claimed that the infection was prenatal, it was almost impossible to absolutely exclude postnatal infection, which of course

renders such evidence of prenatal infection as valueless. Craig cites the negative findings of Bignami, Bastianelli, Caccini, Schaudinn, and Sereni. The author has made frequent examinations immediately after birth of several infants, whose mothers, during the last few weeks of pregnancy, he had been called upon to treat for malaria, demonstrating, in the blood of the mother, the parasites. These examinations included several estivo-autumnal and benign tertian infections, and one case of the quartan type, but he was unable in a single instance to demonstrate the parasites in any of the new-born, although in not a few of them at birth, preceding, and following it, the parasites were detected in the blood of the mother.

PATHOGENESIS.

There have been in the past many theories as to what produced the fever in malarial infections, but without going into a general discussion of these, it may be stated that it is now universally agreed that the cause of the fever is the result of the liberation of a toxin, formed during the intracorpuscular growth of the plasmodia, which takes place with the sporulation of the organism.

PERIOD OF INCUBATION.

Ross and Thomson have shown that the number of parasites necessary to produce clinical symptoms is about 2,000,000,000. It would therefore seem that the period of incubation would be determined largely by the number of sporozoites injected by the infected mosquito, but as a matter of fact, there is a certain uniformity in the period of incubation, depending on the type of the infection. In Table IV, which the author tabulated from a history of inoculations collected from the literature by Ross, is shown the period of incubation after mosquito inoculation; the complete history of each inoculation, which is given by this author in his recent work on *The Prevention of Malaria,* is omitted from these pages, owing to the space required to reproduce it, for, while of certain interest, it is only desired here to show the actual period of incubation, which is of considerable importance to the physician.

This tabulation shows that the period of incubation in the benign tertian varies from 8 to 25 days: the single case of quartan, showing an incubation period of 11 days; while the estivo-autumnal infections show a period varying from 10 to 35 days.

TABLE IV.

Observer.	Species inoculated.	Period of incubation.
Bignami. (1898)	Est.-Aut. (type?).	35 days.
Bastianelli, Bignami, and Grassi. (1898)		
Ibid. (1898)	Tertian.	20 days.
Ibid. (1898)	Tertian.	19 days.
Manson. (1900)	Est.-Aut. (type?).	34 days.
Rees. (1900)	Tertian.	15 days.
Fearnside. (1901)	Tertian.	About 14 days.
Ibid.	Tertian.	Uncertain.
Ibid.	Tertian.	21 days.
Ibid.	Tertian.	15 days.
Ibid.	Tertian.	25 days.
Ibid.	Tertian.	12 days.
Buchanan. (1903)	Tertian.	16 days.
Ibid.	Est.-Aut. (type?).	20 days.
Ibid.	Est.-Aut. (type?).	19 days.
Ibid.	Est.-Aut. (type?).	12 days.
Ibid.	Est.-Aut. (type?).	19 days.
Ibid.	Est.-Aut. (type?).	19 days.
Ibid.	Quartan.	11 days.
Ibid.	Tertian.	14 days.
Ibid.	Tertian.	13 days.
Ibid.	Tertian.	8 days.
Schuffner. (1902)	Tertian.	11 days.
Ibid.	Tertian.	17 days.
Ibid.	Tertian.	17 days.
Jancso. (1905)	Est.-Aut. (type?).	16 days.
Ibid.	Tertian.	15 days.
Ibid.	Est.-Aut. (type?).	12 days.
Ibid.	Est.-Aut. (type?).	10 days.
Ibid.	Est.-Aut. (type?).	10 days.
Ibid.	Est.-Aut. (type?).	After 14 days crescents in blood.
Ibid.	Est.-Aut. (type?).	12 days.
Ibid.	Est.-Aut. (type?).	14 days.
Ibid.	Est.-Aut. (type?).	11 days.
Ibid.	Est.-Aut. (type?).	11 days.

FACTOR IN INTENSE INFECTIONS.

Christophers recently carried on some interesting experiments showing the factor which determines the intensity of an infection. He found that, if he fed mosquitoes (*Culex*) with the blood of sparrows containing but a few gametes, the midgut of such mosquitoes on dissection showed but a few zygotes, and that, when the zygotes were allowed to mature and reach the salivary glands of the insect, there were but a few of the salivary cells infected and that those that were did not contain sporozoites in large numbers. On the other hand, mosquitoes fed with blood from the sparrow containing numerous gametes showed on dissection large numbers

of zygotes in the midgut, and on maturing, the sporozoites were found in immense numbers in all of the salivary cells. In the continuation of this line of research, he found that, by using a certain number of heavily infected mosquitoes, the resulting infections were sufficiently severe to produce death in every instance, and that in all cases the usual period of incubation, consisting of nine days in the moderate infections, was reduced to five days. In using equal numbers of mosquitoes that were scantily infected, or even by increasing the number, he was unable to produce a severe infection, nor was he able to reduce the period of incubation. He concluded that "The amount of infection carried by mosquitoes then depends on the number of zygotes which develop in the midgut, and the number of these in turn depends upon the number of gametes in the blood of the sparrow by which the mosquito became infected. It is easy, therefore, to see that in malaria everything may depend upon the existence of heavy gamete carriers; and if these are present, upon the number of *Anopheles*. Otherwise, the relation of number of *Anopheles* to the amount of fever will not hold good."

A few years ago the author saw in a village, in which malaria was endemic, a number of very serious infections. An examination of the blood of practically all of the inhabitants showed that there were two individuals very heavily infected with crescents. Under appropriate treatment these individuals were freed of these forms, and he has since seen no heavy infections in this place, and is satisfied that the severe cases that previously occurred were infected by mosquitoes that had been biting and feeding on these heavily infected individuals. Wherever, therefore, heavy infections are occurring in a community where such are unusual, it is well to look for the individual source of infection, and when this is done and the carriers put on appropriate treatment, it will be followed by an absence of such heavy infections.

IMMUNITY.

The question of persons being immune to the malarial infections is one that has been discussed pro and con for many years, and there is no doubt that individuals do develop a certain immunity after living for some time in a malarial country and having had repeated attacks. A study of latent carriers in childhood will show the large percentage of individuals who must have been

infected before reaching adult life. Panse in the examination of 2,227 natives of East Africa found the following percentage of latent carriers:

TABLE V.

Age.	No. examined.	No. infected.	Per cent.
Under ½ year	16	6	37.50
Between ½ and 1 year	9	6	66.60
1 year old	25	22	88.00
2 years old	20	17	85.00
3 years old	28	25	89.20
Between 4 and 5	48	34	70.80
Between 6 and 7	84	52	61.90
Half grown children	314	125	39.40
Adults	1,683	258	15.30

Many other observers have reported similar results, so that in those countries showing a high malarial index among the infants and young children, and slowly declining as adolescence is reached, it is reasonable to infer that a certain amount of immunity is acquired by repeated infections. On the other hand, there are evidently some people that in spite of heavy and repeated infections are unable to secure any immunity. Craig examined the blood of 147 children and 45 adults in the Philippine Islands with the following results:

TABLE VI.

Age.	No. examined.	No. infected.	Per cent.
1 to 5 years	40	30	72.50
5 to 10 years	54	20	37.00
10 to 15 years	53	13	24.50
Adults	45	28	62.20

It will be seen by the above that while the percentage of infections decreased from the fifth to the fifteenth years from 72.50 to 24.50 that the percentage in adults rose to the high figure of 62.20. Craig, in discussing these findings, states that he is unable to explain why the rate, although decreasing as the age advances up to young adult life, advances so markedly from then on. He is of the opinion that the examination of larger numbers of adults in that country would probably reduce the percentage of infections as shown in his examinations, but considers it very evident that the Filipino develops little immunity to the infection in spite of repeated attacks.

The above observations of infections in adults has been confirmed by Plehn in West Africa. He examined 84 children and 43 adults with the following results:

TABLE VII.

Age.	No. examined.	No. infected.	Per cent.
Under 2 years	18	17	94
Between 2 and 5	26	24	92
Between 5 and 10	40	34	85
Adults	43	26	60

It may be concluded that, while certain people acquire an immunity following repeated attacks, there are certain sections where the inhabitants do not obtain such. Manson speaks of the natives of Italy, Corsica, Greece, and Turkey failing to derive any immunity in spite of repeated infections.

On the other hand, there are certain races that appear to enjoy a certain natural immunity, such as the Chinese and Malays. Many writers have questioned the immunity said to be possessed by our negroes, but the statistics given in the report of the Surgeon General of the United States Army for the year 1911 (Table VIII) indicate that this race possesses a marked immunity, which is, however, probably acquired in early life following repeated infections.

ENDEMIC INDEX.

It has been usual in the past to consider the malarial index of a community largely in accordance with the percentage of splenic enlargements found among the inhabitants. This has to be discarded in those sections where kala azar is also present, owing to the marked splenomegalia that exists in the latter infection, and which until a short time ago was considered to be nothing but a manifestation of malaria. With the knowledge that kala azar is a disease *per se*, it is plainly evident that, inasmuch as it is accompanied by splenomegalia, this system, as a guide to the malarial index, was on a false basis wherever both the diseases prevail. Table IX prepared by Stephens and Christophers illustrates the fallacy of depending on the spleen rate for the index of malaria, the figures being based on the spleen enlargement rate and the parasite rate:

TABLE VIII.

MALARIAL INFECTIONS, UNITED STATES, CONTINENTAL (EXCLUDING ALASKA), YEAR 1910.

[Ratios per 1,000 of mean strength.]

Malarial fevers.	Admitted.			Discharged on certificate of disability.			Died.			Noneffective.		
	Total.	White.	Colored.	Total.	White.	Colored.	Total.	White.	Colored.	Total.	White.	Colored.
Intermittent:												
1910	14.57	15.18	3.68	.....	.....	.....	.....	.....	.....	0.28	0.29	0.06
1909	20.29	20.74	7.65	.....	.....	.....	.....	.....	.....	.41	.42	.13
1908	24.12	24.33	11.05	.....	.....	.....	.....	.....	.....	.49	.49	.14
1907	28.44	29.28	.96	.....	.....	.....	.....	.....	.....	.53	.54	.02
1906	47.32	49.19	18.53	.....	.....	.....	.....	.....	.....	.93	.97	.39
Estivo-autumnal:												
1910	1.36	1.39	1.00	.....	.....	.....	.....	.....	.....	.05	.05	.03
1909	1.96	1.99	1.02	.....	.....	.....	.....	.....	.....	.07	.07	.03
1908	2.09	2.11	1.38	.....	.....	.....	.....	.....	.....	.08	.08	.04
1907	1.51	1.55	.....	.....	.....	.....	.....	.....	.....	.08	.08	.....
1906	1.87	1.94	.80	.....	.....	.....	0.02	0.03	.....	.10	.11	.03
Malarial cachexia and undetermined malarial infections:												
1910	.43	.46	.....	.....	.....	.....	.....	.....	.....	.03	.03	.....
1909	.80	.83	.....	0.02	0.02	.....	.....	.....	.....	.04	.04	.....
1908	.47	.48	.....	.....	.....	.....	.....	.....	.....	.01	.01	.....
1907	.26	.26	.....	.....	.....	.....	.....	.....	.....	.02	.02	.....
1906	1.08	1.07	1.21	.05	.05	.....	.....	.....	.....	.09	.08	.15
Total malarial diseases:												
1910	16.36	17.02	4.69	.....	.....	.....	.....	.....	.....	.36	.37	.09
1909	23.06	23.57	8.67	.02	.02	.....	.....	.....	.....	.51	.53	.16
1908	26.69	26.91	12.43	.....	.....	.....	.....	.....	.....	.58	.59	.18
1907	30.20	31.09	.96	.....	.....	.....	.....	.....	.....	.63	.65	.02
1906	50.27	52.20	20.56	.05	.05	.....	.02	.03	.....	1.12	1.16	.55

TABLE IX.

Locality.	Spleen rate.	Parasite rate.
Calcutta	0.0	0.0
Jalpaiguri—		
Bustee children	27.0	16.1
School children	14.7	0.0
Babu children	14.2	0.0
Mainaguri	74.0	25.0
Rungamutty	83.0	43.6
Sam Sing	7.1	16.0
Kurseong 1	0.0	0.0
Kurseong 11	0.2	0.0

Ross considers that "there is probably only one really accurate method by which we can determine the degree of malaria in a given locality, and that is by ascertaining the average time in which a newcomer becomes infected." Deaderick considers that the most accurate method to determine the index is to examine a number of children, the percentage of gamete carriers giving the true index. Both of these methods are open to objection. The first will be governed almost entirely by the precautions observed by the newcomer, and it has already been shown that in some communities gamete carriers may be equally as numerous among adults as in children, and in some exceptional instances even more so. The only satisfactory and certain manner, therefore, to determine the index in a given community, is to examine the blood of a large number of inhabitants of all ages.

OLD-TIME THEORIES CONCERNING TRANSMISSION.

Any discussion of the etiology of malaria is not complete without a passing reference to the various exploded theories concerning the transmission of the disease. The full value of the discovery that the mosquito is the carrier of the infection lies in the fact that we also know that it is the only method by which the disease can be contracted. The very nature of practically all these old theories is now seen to be coincident with the established etiological factor. Thus the night air, which was held to be so dangerous in malarial countries, is now known to be harmless provided it does not contain the hungry mosquito intent on a meal of fresh blood. Working in swamps, the presence of "miasmas" or decaying vegetable matter, going into the water in the evening hours, and many other more or less popular theories, held in the past, are now seen to be all concomitant with the presence of the mosquito, because it is in such places that they are found. Probably the most popular theory, and one that held favor for a long period previous to the discovery by

Ross, was that the disease was contracted during the upheaval of soil by the liberation of toxins. It is not hard to convince the most skeptical at the present time that the disturbance of the soil results in the creation of breeding places for the mosquito, and that only in this manner is such soil disturbance a factor in the etiology of the malarial fevers. The segregation of labor at points where extensive earth-disturbing projects are under way often furnishes, in the form of chronic gamete carriers among such laborers, the other necessary factor for an epidemic of the disease, and so it becomes rampant, as a result of these two etiological factors: conditions favoring the breeding of mosquitoes, and the presence of gametes in the circulation of man.

CULTIVATION OF MALARIAL PLASMODIA.

Many investigators have attempted the cultivation of plasmodia in vitro since the discovery of the parasite by Laveran, but the results have been uniformly negative until very recently. In 1911 Bass [1] first announced successful cultivation of *Plasmodia vivax, Plasmodia malariæ*, and *Plasmodia falciparum*. Detailed technic was not given at that time.

In October, 1912, Bass and Johns [2] published a report of successful cultivation of malarial plasmodia from the blood of twenty-nine cases of estivo-autumnal malaria and six cases of tertian in Panama.

In this communication the technic was given in the minutest detail as follows:

TECHNIC.

Apparatus and Material.—The apparatus and material necessary for the cultivation of one generation only of parasites are as follows:

1. Syringe and needle. We use a twenty cubic centimeter all glass syringe with coarse needle. The latter is necessary to avoid strong capillary force and strong suction which so alter the host cells (or parasites), that the parasites often die in a short time. The large needle is also desirable to avoid leaking and bubbling of air into the syringe and to facilitate taking blood into and expelling it from the syringe.

2. Defibrinating tube. Tubes one inch in diameter and of whatever length will be accommodated by the centrifuge (if a centrifuge is to be used) are appropriate. The tube is plugged with a cotton plug having a glass rod running through it and extending to the bottom. We have used with equal

[1] *Jour. A. M. A.*, Vol. LVII, No. 19, p. 1534.
[2] *Jour. Experimental Medicine*, Vol. XVI, No. 4.

satisfaction a glass tube in place of the rod. To this is attached the needle by means of a short piece of rubber tubing. The blood is collected directly into the defibrinating tube by sticking the needle into an infected vein.

3. Culture tubes one-half by five inches.

4. Graduated pipette, one cubic centimeter, graduated in hundredths.

5. Dextrose (Merck's), 50 per cent solution in water.

6. Capillary pipettes and rubber bulb. Three to four-sixteenths of an inch glass tubing is the proper size from which to make these pipettes. The capillary tube should be rather large. Fine capillaries are destructive to malarial plasmodia. The large end of these pipettes should be plugged with cotton before sterilizing.

7. Incubator regulated to a temperature of 40° C.

The following additional apparatus will be required if more than one generation of parasites is to be grown, or if it is desired to avoid the dead parasites which are present in the deeper layers of cultures containing a thick column of cells:

8. Centrifuge. Speed, 800 to 2,000 revolutions per minute.

9. Culture tubes one-half by five inches, with flat bottom or with disk of pure white filter paper supported one-half inch from the bottom of the tube by a piece of glass tubing. The latter should be cut straight across and fairly smooth on the upper end and should fit the culture tube closely.

10. Plain pipettes, capacity five to twenty cubic centimeters, with rubber tube two feet long, mouth piece, and pinch cock. These pipettes are plugged before sterilizing and are used but once on account of the difficulty of cleaning them.

Technic for Cultivating One Generation Only.—Blood is collected from the patient's vein at the bend of the elbow. If drawn with the syringe it is expelled directly into the defibrinating tube. The latter should be tilted to one side and care should be taken to avoid unnecessary exposure of the blood to the air. In either case, one-tenth of a cubic centimeter of the 50 per cent solution of dextrose for each ten cubic centimeters of blood to be taken is placed in the defibrinating tube before the blood is drawn. Defibrination is effected by gently stirring or whipping with the rod or tube which extends through the cotton plug. The whipping in of air, causing bubbles, must be avoided. The plug and rod may now be replaced by a plug from another tube of the same size.

The defibrinated dextrose blood may be transferred to other tubes or incubated in the original tube. In any event the column of blood must be one to two inches deep. This gives a column of serum one-half to one inch deep above the cells and parasites when the latter have settled. Supernatant serum more than one inch deep has no advantage. When this is less than one-half of an inch deep the parasites often die before segmentation occurs. We have occasionally seen perfect segmentation, however, under one-fourth of an inch of serum.

The parasites live and develop at the top of the column of precipitated cells in a layer varying in thickness from one-fiftieth to one-twentieth of an inch. All parasites beneath this layer die in from two to twenty hours; the time is dependent upon factors which we have not determined. Some

grow considerably before they die and we have occasionally seen small rings attain over half the full adult size under these circumstances. When parasites die in these deep cells the central clear space in the small ring closes, or if the parasite is older the irregular projections, pseudopodia, are withdrawn. If pigment is present, it loses its motility. The protoplasm gradually shrinks, losing its staining reaction, and finally only the nuclear chromatin granule remains, and this also stains poorly. In the instance of very small parasites often the red blood cell shows little or no evidence of the previous presence of the parasite.

The parasites in the thin layer at the top of the column of cells develop and may be examined at any time by drawing a small quantity of cells from this layer by means of a capillary pipette. Some considerable practice is required in order to do this without drawing cells and dead parasites from just below this layer. The pipette may be passed through a flame to sterilize it on the outside, but it must be allowed to cool thoroughly before it is used, since, in our experience, a temperature of 45° to 50° C. kills the parasites in a very short time.

Such a temperature also alters the red blood cells in some way so that they are rendered permeable to the surrounding serum, and this effect is destructive to the parasites. Great care must be taken in handling tubes containing cultures to keep them in the upright position. Tilting to the side results in burying and killing the living parasites in the thin layer at the top of the cells which have settled to the bottom of the tube.

Technic for Cultivating More than One Generation.—If more than one generation of plasmodia is to be cultivated, it is necessary to remove the leucocytes when the culture is made in order to avoid destruction of the parasites by them at the time of segmentation. The infected blood from the patient is centrifugalized sufficiently to force the leucocytes to the surface of the cells. The length of time necessary to centrifugalize varies with the speed, length of arm, etc., of the particular centrifuge used and should be determined by experiment. Unnecessary centrifugalization should be avoided.

The supernatant serum is drawn off and put in culture tubes. The column of serum in each should be one-half to one inch deep. Cells and plasmodia are carefully drawn from about the middle of the centrifugalized cells and planted at the bottom of the serum in the culture tubes. Flat bottom tubes are an advantage. One to two-tenths of a cubic centimeter of cells in a half-inch tube make the thickest layer in which it is possible to get a homogeneous growth of parasites. We have been able to secure growth of all the parasites in about twice this quantity of cells in a half-inch tube by employing tubes with a paper shelf suspended in them. They are filled with serum to at least half an inch above the level of the support for the paper disk. The disk is then carefully tucked in place, after which the cells are placed on it.

We have obtained even more satisfactory results with tubes filled one-half inch deep, or more, with freshly prepared human plasma. These are conveniently prepared by placing one-half to one inch of blood, immediately after it is drawn, in culture tubes and centrifugalizing to throw the cells to the bottom before coagulation takes place. By continuing centrifugaliza-

tion until after coagulation occurs, a flatter surface is secured for the plasma than if it is discontinued before this time. In such plasma prepared tubes one-half inch or more of serum is placed and then cells and parasites from the centrifugalized and defibrinated dextrose blood are carefully distributed over the surface of the plasma. We have sometimes obtained in these tubes a layer of live parasites approximately one-tenth of an inch thick.

Parasites in such leucocyte-free cultures develop, segment, and most of the merozoites enter new red blood cells. These young parasites develop in the same manner as the first generation and sometimes reach the stage of segmentation. In fact we have in one instance observed the development of three successive generations in such a culture. More often, however, the parasites begin to die out after the first segmentation and especially after the second. We have not been able to determine exactly the cause of this. In order to perpetuate the culture it is necessary to transfer a portion of the cells and parasites to a recently prepared tube containing fresh cells and serum. It is convenient to place the fresh serum in the culture tube and to take up in a large capillary pipette a portion of the cells and parasites of the culture and then about five times the amount of fresh cells. These are mixed in the pipette with air excluded and then carefully spread on the surface of the plasma, paper shelf, or bottom of the tube, according to the particular kind of culture tube used. The transplantation should be done within four or five hours of the time of maximum segmentation and therefore approximately every forty-eight hours for tertian and estivo-autumnal parasites.

The work of Bass and Johns has been confirmed by Lavinder in America; and Ross, Thomson and others in England. These different workers have successfully cultivated the parasites according to the technic given and it will now be possible to study various questions related to malaria and malarial plasmodia in the test tube.

FACTORS DETERMINING THE AMOUNT OF MALARIA IN A GIVEN COMMUNITY.

From what has been gathered from the foregoing pages concerning the etiology of this disease it becomes apparent that the amount of malaria in a given community depends on three factors: the number of *Anophelines* present; the number of infected individuals from whom the mosquitoes are able to contract the infection; and the opportunities accorded the mosquito to bite man, resulting in the twofold process of their contracting the infection, and transmitting it. Ross in an elaborate system has worked out conclusions, largely by considering the laws of chance, on the likelihood of a given number of healthy persons, having among them a given

number of infected individuals, contracting the infection, with a given number of *Anophelines* also present. He has elaborated on the necessary factors as follows:

(1) That a person whose blood contains a sufficient number of gametids (sexual forms) is living in or near the locality.

(2) That an anopheline capable of carrying the parasites sucks enough of that person's blood.

(3) That this anopheline lives for a week or more afterward under suitable conditions—long enough to allow the parasites to mature in it.

(4) That it next succeeds in biting another person who is not immune against the disease or is not protected by quinin.

The author wishes to draw attention to and to especially emphasize the fact that the significance of the number of gamete carriers has been almost lost sight of in considering the number of *Anophelines*. One is equally as significant as the other: a large number of *Anophelines* with a small number of malaria-infected individuals holds the same relation toward the endemicity of the disease as a large number of gamete carriers with a small number of *Anophelines*. Ross presupposes that the likelihood of mosquitoes succeeding in reaching man as being one chance in four, so that with a single *Anopheline* present and one infected person, in say a population of one thousand, the chance of this single mosquito becoming infected by biting the single infected person, if it succeeds in reaching man at all, is one in four thousand. In continuing his deductions, this author shows that the next factor that has to be considered is the probable life of the mosquito. It must live a week or longer to be capable of transmitting the infection, and he places the chance of the mosquito's doing this as one in four, this reducing the likelihood of the insect's maturing the infection to one in twelve thousand. Now, it has to bite another person, and the chance is, of course, the same as prevailed for the first biting, namely, one in four, making the total chance of an *Anopheline* succeeding in contracting and transmitting the infection as one in forty-eight thousand, in a community of 1,000 people containing one gamete carrier and one *Anopheline;* but such a condition could of course never exist in fact, as mosquitoes wherever present are in large numbers. It does not require much knowledge in mathematics to figure out, with the above illustration as a working basis, the likelihood of a given number of mosquitoes, with the presence of a given number of

individuals carrying the sexual forms, being able to inoculate a given number of non-infected persons, and it emphasizes the fact that the presence of malaria, in either endemic or epidemic form, is necessarily governed as much by one factor as the other. There are many communities where the eradication of the mosquito is an almost hopeless task, and impractical, owing to the immense funds that would be necessary not only to eradicate them for a single season but to keep them continually eradicated, but it is within the power of any physician to eradicate the sexual forms of the parasite in man. Too much work, therefore, cannot be done toward the education of the public, not only on the rôle played by the mosquito, which is now generally accepted, but on the equally significant rôle played by man, which is understood very little if any by the average layman, and largely neglected by the physician in the treatment of his cases of malaria. This will be discussed at length in the chapter on the prophylaxis of the disease, and the significance of latent malarial infections as a predisposing etiological factor will be covered in a chapter devoted to latent malaria.

CHAPTER V.

PATHOLOGY—COMPLICATIONS—SEQUELÆ —PROGNOSIS.

PATHOLOGY.

The pathology of malaria is especially characterized by changes in the blood, the other important changes, which are more or less pronounced, depending on the type and severity of the infection, being seen in the spleen, liver, kidneys, brain, bone marrow, and the intestinal tract.

Entering largely into the pathological changes occurring in the malarial infections is the distribution of melanin and hemosiderin. The former is derived from the hemoglobin as a result of the action of the parasites on this blood constituent during intracorpuscular life. It is of a deep-brown or black color and is distributed within the blood, either free in the plasma, the plasmodia contained within the red cells, or the leucocytes, and also within the tissues. It is liberated at the time of sporulation of the parasites, is insoluble in acids, is free from iron, and freely soluble in sulphid of ammonium. Hemosiderin, on the other hand, is derived from the hemoglobin of broken-down red cells, other than those destroyed by the plasmodia. It is of a yellowish color, insoluble in acids, and contains iron. It is not found in the blood-stream, being deposited only in the tissues.

Blood.—The very nature of the disease, the parasites attacking the red corpuscles, is such as to produce very great changes in the blood. The destruction of the corpuscles with the accompanying loss of hemoglobin rapidly produces an anemia, as a reduction in red corpuscles follows each paroxysm. Thayer states that "these reductions are more marked after the early paroxysms than after those occurring later. When a certain degree of anemia has been reached the losses per paroxysm are much less. When the number of corpuscles is reduced to 2,000,000 or 1,000,000, there is little tendency toward a further fall; sometimes there may be slight rises

in the curve between the paroxysms; often, however, the number of corpuscles remains stationary for weeks. In pernicious cases the number of corpuscles may fall between paroxysms."

The rapidity with which this reduction is accomplished is very marked. Craig has observed a loss of 2,000,000 red cells per cubic millimeter within thirty-six hours in a case of tertian estivo-autumnal infection, and cites the cases of Turck with a loss of 1,000,000 in one day, Mannaberg's with 1,000,000 in two days, and Kelsch's with 2,000,000 in two days, all of them being with the estivo-autumnal infections; and Grawitz records a case showing a loss of 4,000,000 red cells in six days. The author recently saw a case of tertian estivo-autumnal in a child two years old, where the red cell count was reduced to 2,000,000 per cubic millimeter in six days. The destruction of red cells is accompanied by a marked reduction of hemoglobin, which in severe cases may amount to 40 per cent in a few days. This loss is not entirely due to the hemoglobin destroyed in those red cells attacked by the parasites; there is also a loss in those cells that do not become infected with parasites, apparently due to some toxic agent, of which fact "there is additional evidence in the polychromatophilia and granular degeneration of the body of the red cell so often present in severe malarial infections." (Delafield and Prudden.)

The changes in the size, color, and form that occur in the erythrocytes have already been discussed in the description covering the various species of the plasmodia.

Leucocytes.—There is in nearly every malarial infection, except pernicious cases, whether of recent or old origin, a leucopenia, the leucocytes being reduced to 3,500, or even to 2,000, per cubic millimeter. This reduction may be preceded early in the infection by a leucocytosis which is present only for a short time; in pernicious cases, however, leucocytosis may prevail, a count of 20,000 to 30,000 per cubic millimeter being commonly observed. The white cells are frequently pigmented with granules of melanin. A differential count will often prove of great value in arriving at a diagnosis, as the lymphocytes will always be found very much in excess, the large mononuclears being especially numerous. The polynuclears and eosinophiles are reduced, especially the latter; a malarial infection presenting evidence of eosinophilia is suggestive of an accompanying intestinal helminthiasis, a common coincident infection in countries where both diseases prevail.

In 204 cases Krauss found the following differential count to be the average:

	per cent
Small lymphocytes	14.8
Large lymphocytes	19.5
Polymorphonuclears	63.7
Eosinophiles	2.0

Craig gives the average differential count in the various types of the infection as follows:

	per cent	
Polynuclears	52.0	Count in tertian malaria.
Small mononuclears	16.3	
Large mononuclears and transitionals	32.4	
Eosinophiles	.3	
Polynuclears	52.0	Count in quartan malaria.
Small mononuclears	20.6	
Large mononuclears and transitionals	22.2	
Eosinophiles	3.0	
Polynuclears	45.0	Count in estivo-autumnal infections.
Small mononuclears	18.4	
Large mononuclears and transitionals	5.0 35.6	
Eosinophiles	1.0	

Note the low count of eosinophiles in the benign tertian infections, the increase of 50 per cent above normal of these cells in the quartan infections, and the equal decrease from normal in the estivo-autumnal infections. The polynuclear count is relatively the same in all types of the infection, being slightly lower in the estivo-autumnal types. The difference in the small mononuclears is not marked, but the changes occurring in the large mononuclear count are especially so. Very high in the benign tertian, they are not quite so numerous in the quartan, reaching more nearly normal in the estivo-autumnal, while in the latter the count of transitionals reaches an exceedingly high mark.

Spleen.—This organ is nearly always more or less enlarged. In the tertian infection it is especially so, particularly following repeated attacks, but in estivo-autumnal infections this enlargement is not so marked, there often being but slight splenomegalia, excepting in old long-standing cases.

This enlargement in rare instances becomes so pronounced as to cause spontaneous rupture of the organ. Rupture may also follow puncture of the gland for diagnostic purposes, and on this account the procedure is not devoid of danger. Thayer speaks of a case in which this accident occurred following aspiration for diagnostic purposes, similar cases being reported by others. The spleen is of a dark-slate color or sometimes even black, caused by the pigment derived from the parasites and degenerated red cells. The pulp often becomes soft, sometimes assuming a diffluent character; it contains many red cells with the older forms of the parasites within them; the younger forms may also be present but are not so numerous as the older ones. The pulp sinuses contain free pigment, both melanin and hemosiderin being observed, the former a dark-brown or black color, the latter a golden-yellow. Areas of necrosis may be present. On section it appears a slate color, which in old infections is sometimes deepened, becoming almost black. The capsule becomes very much thickened as the infection persists, and is adherent to the surrounding tissues. The Malpighian bodies, not well marked early in an infection, become so in long-standing or repeated ones, or in improperly treated cases. The trabeculæ are markedly hypertrophied and usually contain pigment, the connective tissue being increased. The venous sinuses become congested, and contain numerous plasmodia, both intracorpuscular and extracorpuscular, pigmented leucocytes, and macrophages, phagocytosis being actively carried on by the latter. It has generally been held that in the estivo-autumnal infections crescents are especially numerous in this organ. Craig, however, states that he has never found them in any great numbers, and that they are often absent when they can be readily demonstrated in the peripheral blood. He reports two fatal cases of the disease in which long and patient searches were required to demonstrate the parasites in smears taken from this organ, and cites the case of Bloombergh and Coffin in which no plasmodia could be found in sections of the spleen but were demonstrated in the peripheral blood.

Liver.—This organ usually becomes enlarged and is very much congested, presenting a dark-brown or black color, due to the deposit of melanin and hemosiderin. The consistence of the organ is generally diminished, and the liver cells become swollen, contain hemosiderin, and in old-standing cases hypertrophy, or may be supplanted by connective tissue. The endothelial lining of the capillaries are

studded with pigment, while the capillaries themselves contain numerous plasmodia and macrophages, the latter reaching very large sizes. Areas of focal necrosis may be present following intense infections with the estivo-autumnal types of the disease. On section the cut surface of the organ oozes blood, the congestion being very great. The gall-bladder is distended with dark-brown or black bile.

Kidneys.—The changes taking place in the kidneys are not very marked except in severe cases. In these, it is believed that the changes that do occur are the result of some toxic substance in the blood rather than to the direct action exercised by the plasmodia within the organs. In repeated or severe infections the kidneys appear as slightly enlarged, and more or less congested, depending on the severity of the case. The capsule is not adherent. The Malpighian corpuscles are congested and contain hemosiderin, the epithelium of the convoluted tubules undergoes degeneration, and the straight tubules contain epithelial, hyaline, and granular casts. The glomeruli and intertubular capillaries may contain melanin, small numbers of parasites, leucocytes, and macrophages. In pernicious cases the pathology of the kidneys may be that of an acute parenchymatous nephritis.

Brain.—Except in pernicious malarial infections, the brain presents few pathological changes. In severe cases, especially those that take on cerebral symptoms, the meninges are infected, congestion being marked; there will often be seen areas of punctiform hemorrhages, and the capillaries may contain immense numbers of plasmodia in different stages of development, in addition to pigmented leucocytes, macrophages, and endothelial cells. The endothelium of the capillaries may be studded with both parasites and free pigment and may undergo fatty degeneration, while the cortex of the brain may appear almost black from pigment deposit.

Bone Marrow.—This will vary in color from a pinkish to a deep brown or black, depending on the length of time the infection has been present and its intensity. It contains numerous pigmented parasites, and the sexual forms of the estivo-autumnal infections are especially numerous. The marrow substance sometimes becomes diffluent and contains a large amount of pigment, and numerous macrophages. The capillaries may contain a larger number of plasmodia, much free pigment, and many pigmented macrophages.

Intestinal Tract.—The pathological changes occurring in the in-

testinal tract are not marked except in exceptional instances. Cases presenting choleriform symptoms are more apt to be followed by pathological changes, consisting of highly congested blood-vessels containing numerous plasmodia within the red cells. Their endothelial lining may be severely pigmented and may undergo degenerative changes, sometimes resulting in thrombosis, necrosis, and hemorrhage.

COMPLICATIONS.

Pneumonia.—Pneumonia is a very common complication of malaria and is so often present that, previous to the discovery of the plasmodia, it was considered as a manifestation of malarial infection. Both lobar and bronchopneumonia may occur, but the former is the more usual type present as a complication. It is more often seen in the estivo-autumnal infections and adds very much to the gravity of the prognosis, the mortality in such complicated cases reaching 50 to 75 per cent. The pneumonic symptoms will usually overcome those of the original infection, although in some instances the clinical picture of pneumonia is much altered as a result of sporulating plasmodia.

An acute bronchitis is also a common pulmonary complication.

Dysentery.—Dysentery, both specific and amebic, are very common complications. In the United States Army General Hospital at San Francisco 65 per cent of soldiers suffering with malarial infections, and who had recently returned from service in the Philippine Islands, were found, by Craig, to be also suffering from dysentery. In 25 per cent of these cases he demonstrated the *Entamœba histolytica*. All cases developing dysentery should undergo a careful examination to determine its origin, as it is common to see such attacks in latent malarial carriers, and if such examination of the feces proves negative, it is evidence of the fact that the dysentery is due to the malarial infection. In such cases the dysenteric symptoms will rapidly subside under appropriate malarial treatment, and to the exclusion of any other line of treatment. The author has seen many cases of intestinal disturbance, varying from a mild diarrhea to a severe dysentery, that failed to respond to any of the usual treatments for such conditions, but that rapidly recovered under quinin.

Typhoid Fever.—While it is unusual to see malarial organisms remain in an active state throughout the course of a typhoid in-

fection, they are frequently present during the first few days of the invasion, and their presence will often for a time render a positive diagnosis impossible. Craig has reported a case of coincident quartan infection which persisted throughout the course of a typhoid illness, and two cases of combined typhoid and estivo-autumnal malaria. Such infections are however rarely seen together, and while in malarial districts typhoid fever patients will often harbor the plasmodia in an active state during the first few days of the disease, their activity will be overcome early in the course of the infection. They will often reappear during convalescence from typhoid but are seldom seen all through its clinical course, but in spite of this fact, it is not unusual in certain sections of this country to hear the crude diagnosis of "typho-malarial fever." This term, never worthy of a place in the vocabulary of an educated physician, should forever be relegated to the rear. It would be just as absurd to refer to a condition as "diphther-malarial," where malarial parasites were found in the blood of a child ill with diphtheria, as to apply the term typho-malaria to those cases showing malarial parasites in a beginning typhoid attack. Care should always be taken to give the proper significance to the presence of malarial organisms in the blood, not forgetting that they may be but concomitant with some other pathological condition.

Tuberculosis.—It is often impossible to differentiate between an incipient tubercular lesion and chronic malaria from the clinical picture alone. It was formerly held that the two diseases could not coexist, but this has proved to be an error. In fact, the loss of resistance, as a result of repeated malarial attacks, or from the chronic forms of the disease, renders such individuals particularly prone to all tubercular infections. The negro of the Southern states is peculiarly susceptible to tuberculosis, and the author has seen many cases that were apparently induced by neglected malaria.

Pregnancy.—It is a very common occurrence to see women during the lying-in period develop active malarial manifestations, where the disease has been in a latent state, possibly for many months or longer. It is a complication of the puerperal state that may give the attending physician considerable anxiety, and an examination of the blood for plasmodia should be conducted before deciding on treatment.

Abortion.—Abortion and premature labor are common and serious complications of malaria. The percentage of pregnant women that

will abort following malarial infection will depend largely on the type of infection that prevails, the complication being greater where the estivo-autumnal are the prevailing infections than where the tertian or quartan predominate. The author does not think that 25 per cent is too high a figure to place on this complication, where the estivo-autumnal infections are present, but the outcome necessarily largely depends on treatment, which will be discussed later.

Nephritis.—Nephritis is also a very common complication. It may occur during the acute stages of an infection, but is more often seen among the old sufferers of the disease. The frequency of the complication is given by various authorities in widely varying figures. Thus, Moore states that it is 80 per cent, and Thayer, that in the benign tertian and quartan infections it is 38.6 per cent, and in the estivo-autumnal types 58.3 per cent. Craig confirms these figures on the tertian and quartan, but has found, in his observations, that in the estivo-autumnal infections nephritis is present in 65 per cent of them. On the other hand, Deaderick and Ford both place the complication as of rarer occurrence, 2 per cent or less being their figures, and there is no doubt that it varies a great deal under varying conditions. Where the original infections are promptly treated, or where the infections are less intense, this and all other complications will necessarily be fewer than when the disease progresses for a time with little or no treatment, or in those districts where intense infections prevail.

Heart Diseases.—Valvular lesions of the heart may complicate malaria, rendering the prognosis a very grave one. A tachycardia, entirely out of proportion to the height of the fever, may be present, and during convalescence, bradycardia may be present for days, the pulse often being as low as thirty-five or forty.

Hookworm Disease.—Of especial significance in the Southern states is the coexistence of uncinariasis and malaria. The author has seen many instances, where children suffering from hookworm disease failed to improve following proper treatment, in spite of the fact that their feces became negative, and that blood-constructive tonics were administered. In many such instances he demonstrated the presence of malarial plasmodia, which had not been looked for in the enthusiasm of curing the other infection, and following the administration of quinin they rapidly improved. The pathology of the two diseases renders an individual infected with one very susceptible to the other, and there is no doubt that many

cases of hookworm disease result fatally, on account of a complicating malaria, too often overlooked. It is also equally true that, in many cases of malaria, a coexisting hookworm infection is overlooked, and the author would impress the necessity of a careful examination of both blood and feces of patients in whom we suspect either infection.

The chronic nature of the disease when it is not properly treated, which unfortunately is the rule and not the exception, renders complications with almost any disease very likely, and we shall not discuss them separately. All of the infectious diseases, gonnorhea and syphilis, in fact all of the ailments the human race is subject to, may be and often are coincident with malarial infection.

SEQUELÆ.

The sequelæ of malaria are those that would naturally be looked for in such pathological conditions as are produced by the disease.

In the Blood.—Anemia is a constant sequela to repeated infection, and while it does not often remain long following original attacks, where the blood-producing organs are not altered, it is necessarily persistent in those having recurring or repeated infections. The changes occurring in the blood have already been discussed in considering pathology, and will not be dwelt on further here.

In the Genitourinary System.—Nephritis is a common aftermath of repeated malarial infections. To malaria, more than to any other disease, can be attributed the high mortality rate from this affection, so common in all tropical and subtropical countries. It will but seldom occur after but a few attacks of malaria, but in repeated cases or in those that are not treated a sufficient time to entirely eradicate the infection, and in whom it remains latent, it is of very great frequency.

In the Glandular System.—Splenomegalia is a constant sequela to chronic malaria, and is present more or less following each acute attack. It will not persist, except after repeated attacks, or in those improperly treated; in such cases, however, the spleen may attain enormous size. Craig reports having seen two cases of spontaneous rupture of this organ, Banta reports a case, and Palmer records one in which rupture occurred within seven days of the initial symptoms of the disease. Other cases have been reported.

The liver becomes enlarged following repeated infections and remains in a hypertrophied state, but in most cases the functions of

the organ do not seem to be retarded. The author has seen two cases of cholecystitis which seem to have undoubtedly been brought on by malaria; in each instance the gall-bladder was drained, and the patient made an uninterrupted recovery.

These are the most common sequelæ of repeated malarial attacks. It should be borne in mind that the debility produced by this infection, when it is allowed to persist, is marked, and that these unfortunates become easy prey for almost any other disease, and that in this manner malaria acts as a contributory cause to the general morbidity and mortality rates in districts where the disease prevails. It has been frequently shown that, following an active campaign against this disease, the accompanying decline in morbidity and mortality rates is not confined to malaria, but that a very general improvement in the health of the inhabitants follows upon the wake of such campaigns, which is well illustrated in the following table given by Ross:

TABLE X.

1. Cases of Malaria admitted to Klang Hospital from the Two Towns compared with those admitted from the District.

Years	1901	1902	1903	1904	1905
Towns	610	199	69	32	23
Districts	197	204	150	266	353

2. Deaths in Klang and Port Swettenham.

Years	1900	1901	1902	1903	1904	1905
Fever	259	368	59	46	48	46
Other diseases	215	214	85	69	74	68

3. Deaths registered in District, excluding Towns.

Years	1900	1901	1902	1903	1904	1905
Fever	173	266	227	230	286	351
Other diseases	133	150	176	198	204	271

(In the above tabulation the Towns referred to are Klang and Port Swettenham, in which active measures against malaria were commenced in 1902, the Districts referred to being the immediate surrounding territory, in which no measures were taken.)

PROGNOSIS.

It may generally be stated that the prognosis of the benign tertian and quartan types of malaria is always favorable, provided treatment is instituted, and even in those cases that are not properly treated, fatalities are rare, excepting in young children and infants. It should be borne in mind, however, that fatalities may occur in even a benign tertian infection when complications accompany the disease. The quartan infections, especially persistent, may act as a chief contributory cause of death if not properly treated. In all those cases, however, in which quinin is administered, even if not continued a sufficient time to entirely eradicate the infection, recovery is the rule. However, even the benign tertian infections are

responsible for many deaths among young children and infants, where a diagnosis is not arrived at until the infection has persisted for some days. The blood-producing organs, in these young children and infants, have not the power of accommodation that they have in adults, so that, in addition to overwhelming these little ones with toxins generated by the parasites, their tissues suffer from want of oxygen as a result of the destruction of the red corpuscles; and the author has seen many deaths from uncomplicated tertian infections in children under one year, where the infection had been active for some days before treatment was instituted. On the other hand, infants and young children tolerate quinin better in proportion than do adults.

In certain cases, while the asexual forms of the plasmodia may be in such small numbers as to produce clinical symptoms for but a short time, gametes may form in large numbers, and we have already adduced evidence that the intensity of an infection, on which the prognosis necessarily depends, is influenced entirely by the presence of heavy gamete carriers. Craig, in discussing prognosis, calls attention to a fact that has often impressed the writer. A study of mortality statistics, as compiled by the Bureau of the Census of the United States, will show that many cities of this country have apparently a very high death rate from malaria, when as a matter of fact, the disease is not at all general in some of them. Those familiar with conditions in the Southern states, while recognizing that the disease prevails in rural communities, and to a certain extent also in the centers of population, to a point that is not a matter for national pride, are perfectly well aware that the apparent high mortality rates given the Southern city as being due to malaria are not in accord with the facts. Thus the statistics issued by this bureau give the following cities a death rate from malaria per 100,000 population as in the following table:

TABLE XI.

Year.	Savannah.	Key West.	Wilmington.	Charleston.	Memphis.	Norfolk.
1904.....	104.5	35.3	205.1	46.3	138.8	17.7
1905.....	154.5	19.5	116.6	42.7	122.1	22.4
1906.....	100.6	28.3	130.1	35.5	118.4	28.4
1907.....	111.6	22.9	74.0	24.8	100.9	26.3
1908.....	122.3	13.3	64.5	44.3	96.5	20.0

That such statistics are grossly incorrect is self-evident. For instance, the malarial death rate given Savannah, in 1908, is 122.3, which means that in a city of 71,000 (the estimated population of

Savannah for that year was 71,163) there occurred some 86 deaths from malaria, which, admitting a mortality of 1 per cent in the total number of cases, means that there were some 8,600 cases of malaria during the year. These errors are doubtless due to incorrect diagnoses, and Craig, in commenting on this situation, writes: "Nothing could illustrate more forcibly the immense importance of a scientific diagnosis of malarial fevers by an examination of the blood than does this quotation, and the condition of ignorance of the true nature of malaria which it portrays is a reproach to American medicine."

The prognosis in estivo-autumnal fevers is good in treated cases, but when oft-recurring, or improperly treated, pernicious symptoms may develop with little or no warning, when the prognosis becomes extremely grave.

It should be borne in mind that, while the prognosis in any given number of cases is favorable, there is probably no other disease that is so often a contributing factor to other illnesses, resulting fatally, as malaria, and that vital statistics from any source do not ever fully record the extent to which it is a contributory cause of existing mortality rates wherever the disease prevails.

The following table given by Deaderick shows the mortality in various parts of the world, as recorded by various observers:

TABLE XII.

Author.	Locality.	Cases.	Deaths.
Laveran	Turko-Russian War	140,000	1,092
Laveran	Constantine	1,310	
Laveran	Italian Army	4,856	13
Schellong	New Guinea	1,954	22
Ross	Greece	960,048	5,916
Ross	Hong Kong	7,352	984
Ewing	Camp Wikoff	605	39
Smart	Civil War	1,373,355	15,423
Travers	Malay States	3,397	348
Terburgh	Dutch Indies	2,308,128	114,490
Cardamatis	Athens	22,618	15
Koch	Grossete	281	
Koch	East Africa	63	2
Hagen	Papua	301	23
British Colonial Reports	British Colonies	12,617	618
Wright	British Malaya	17,468	680
Haw	Baberton	449	14
Hope	North Bengal	1,784	
Laveran	Algiers	98,774	7,432
Gorgas	Panama	1,055	5
Erni	Dutch Indies	116,879	731
United States Marine Hospital	General	6,618	20
Various Hospital Reports	Southern States	1,294	30
German Protectorate Reports.	German Protectorates	5,003	32
Malaria Society	Italy	22,792	120
		5,109,001	148,055

CHAPTER VI.

DIAGNOSIS.

Manson writes: "There is a marked tendency to regard and diagnose all fevers occurring in tropical countries, or in individuals who have returned from tropical countries, as malarial. Such slovenliness in diagnosis must be strenuously avoided by the practitioner. It is apt to become a habit which, sooner or later, is bound to have disastrous consequences."

It is doubtful if there is any disease so often incorrectly diagnosed as malaria. The error is made in both directions, many cases presenting irregular types of fever being classed as malaria, when some other pathological condition is responsible for the symptoms; and on the other hand, many cases of malaria remain unrecognized, in which the disease takes on irregular forms, owing to complications, the presence of more than one group of parasites, or other conditions, such as improper treatment. In cases presenting typical symptoms even the most ignorant tyro can hardly fail to recognize the disease, but there are many cases in which all methods at our command are necessary to establish a diagnosis.

In a great majority of cases in which quinin has not been taken before an examination of the blood is made, such an examination will at once clear up the diagnosis, but the mere presence of plasmodia in the blood should not stop the clinician from looking for other possible existing pathological conditions, nor should a single negative examination satisfy one that malaria is not present. In those cases in which there are more than one group of parasites, often nothing but a microscopical examination of the blood will suffice to establish a correct diagnosis.

There are two methods by which a diagnosis of malaria is arrived at: clinical, and microscopical. Most writers in the past have included, in addition to these methods, the quinin test, a therapeutic test method, in which a fever responding to quinin is classed as malarial, and one giving a negative reaction to the drug, as not of malarial origin. The author considers it a most pernicious habit

to rely on this therapeutic test in the diagnosis of suspected malaria, and the reason for taking such a stand is obvious. When a person presents himself for treatment it is important that a correct diagnosis be established, so that treatment can be instituted, which will not only remove clinical manifestations, but insure the absolute elimination of the infection, thus making it impossible for him to later infect other mosquitoes. There are many fevers, other than malaria, that will respond to the action of quinin, and many more that are self-limited, so that in cases where a disappearance of symptoms may follow the administration of quinin, the fallacy of calling them malaria is apparent.

Again, most writers have justified a diagnosis of malaria, from the clinical picture. While in some instances circumstances may be such that we have to rely on the clinical picture alone, the time has come when nothing but a microscopical diagnosis should satisfy the practitioner, whenever it is possible to secure one. The oft-repeated statement, that the busy practitioner has not time to examine the blood of his fever patients, is ridiculous, and unworthy of anyone engaged in the practice of medicine. It would be just as absurd to make a statement that one has not time to make an urinalysis; for a blood examination for the detection of plasmodia can usually be completed within a very few minutes in a great majority of cases, and is simplified by the application of the thick-film process for the detection of parasites, while, in those few cases that possibly do require more time than the general practitioner can give, a proper examination can be secured without any expense, at least in most of the Southern states, and in a great majority of other sections where malaria is prevalent, from the State Boards of Health, or other health authorities. A physician who has a small income may think that he cannot afford a microscope for such work, but the reverse is the truth; he cannot afford to be without one, and while it is not desired to commercialize this discussion, he will find that he can actually put his microscope to work in helping him earn a livelihood.

The possibilities for error in the clinical diagnosis of malaria are so great, and the effect of failing to make a correct diagnosis so far reaching, that the author believes with Craig, who writes: "I believe that the time will come when it will be considered malpractice to neglect the blood examination in fever cases, and that he who loses a patient from malaria and has not recognized the disease

because of the neglect of a blood examination will be amenable to the law."

CLINICAL DIAGNOSIS.

The clinical division that is generally followed, and to which the author will adhere, is that of tertian malaria, depending on the sporulation of the *Plasmodium vivax;* quartan malaria, depending on the sporulation of the *Plasmodium malariæ;* tertian estivo-autumnal malaria, depending on the sporulation of the *Plasmodium falciparum;* and quotidian estivo-autumnal malaria, depending on the sporulation of the *Plasmodium falciparum quotidianum.* Each of the clinical pictures, resulting from the benign tertian and estivo-autumnal tertian, show particular characteristics, depending on the type, and need in nowise be confusing, although the sporulation of both these parasites occurs every forty-eight hours.

It is generally thought that the estivo-autumnal infections are characterized by fever of a remittent type; this is, however, incorrect, and it may generally be stated that all malarial infections are accompanied by an intermittent fever, when uninfluenced by complicating conditions. Craig in commenting on this point writes: "The impression that prevails among many physicians, that a remittent temperature curve is characteristic of all estivo-autumnal infections, is a false one, for irregularity or remittance is by no means confined to the estivo-autumnal infections, which, if uncomplicated, are as truly intermittent as are either the benign tertian or quartan fevers."

In tertian malaria the *Plasmodium vivax,* sporulating every forty-eight hours, gives a very typical clinical picture, except in complicated cases, in those having more than one group of the parasites, or in cases having received small doses of quinin. This drug will often cause the picture to vary to such an extent that a diagnosis from clinical symptoms is almost impossible.

The chill occurring every forty-eight hours, followed by a temperature ranging from 103° to 106° F., depending on the intensity of the infection, and the susceptibility of the patient, is sufficient to warrant a clinical diagnosis of tertian malaria. The periodicity of the chill, which will usually occur at the same hour of the day as the preceding one, the rapid rise of temperature, with the stage of decline following in a few hours, accompanied by profuse sweating, is a picture that cannot be mistaken.

In quartan malaria the parasite takes seventy-two hours to complete its cycle within man, so that what has been said of the clinical diagnosis of tertian malaria is even more marked in this type of the infection. The exacerbation of clinical symptoms occurring every fourth day makes the clinical diagnosis of quartan malaria an easy matter in single uncomplicated infections. On the other hand, periodicity is very irregular in quartan malaria except in single infections, so that the clinical diagnosis of this type is not satisfactory except under the most typical conditions.

In no type of malaria is a clinical diagnosis more unsatisfactory than in the estivo-autumnal infections. The chill, accompanying the sporulation of the tertian and quartan plasmodia, is often absent entirely in the estivo-autumnal types, and even when present is usually nothing more than a chilly sensation, which may accompany or precede fever produced from almost any infection. The author has found that in the great majority of tertian estivo-autumnal infections there is no initial chill but that the temperature curve is very characteristic. While the temperature will come down to normal between paroxysms, it only remains there for a short time before the succeeding sporulation causes it to rise again. It is of course absolutely impossible to diagnose either of the estivo-autumnal infections from the clinical symptoms when complicated by a benign tertian or a quartan infection.

In the quotidian estivo-autumnal infections the chill is more pronounced than in the estivo-autumnal tertian, occurring every twenty-four hours, followed by an elevation of temperature, and is sufficient upon which to base a clinical diagnosis in localities where it is known to be present.

From the foregoing, it will be seen that periodicity, on which the clinical diagnosis of all types of malaria is dependent, may be interfered with by the previous administration of quinin, the presence of double, multiple, or mixed infections, and by complications.

The *bête noir* of the physician, in trying to arrive at a diagnosis of malaria, is the use of quinin in some form by the patient before presenting himself for examination. What would in many, in fact in nearly all, instances be an easy task is often made a comparatively hard one by the use of this drug, taken in insufficient dosage to give much relief to the sufferer, but sufficient to very materially change the clinical picture of the disease. In a simple benign tertian infection, instead of a chill occurring with typical regu-

larity every forty-eight hours, and followed by fever and sweating, there may be nothing but a history of an initial chill, with irregular forms of fever, occurring at irregular intervals. The fact of having taken quinin will often be denied, but careful questioning will elicit the fact that some of the various so-called "chill and fever tonics" have been taken. These preparations, none of them having enough quinin to eradicate the infection, in many times the dose instructed to be taken, do, however, contain enough of the drug to materially alter the clinical picture.

In double, multiple, or mixed infections it is evident that the presence of more than one group of parasites will cause variations in the clinical picture. Thus a double tertian, instead of having a paroxysm every forty-eight hours, will have an exacerbation of clinical symptoms every twenty-four hours. A double quartan presents a very irregular clinical picture, depending on the time of sporulation of each set of parasites, whereas in a single infection of this type the clinical course is a very distinct one. It is not necessary to describe in detail all of the other various irregular clinical pictures that the disease may assume under such conditions; for such variations depend entirely on the time of sporulation of the different groups of parasites, and it is an easy matter for the reader to figure out what each particular combination will result in clinically.

Double infections of the benign tertian type are of common occurrence, as also are mixed infections of the benign tertian and estivo-autumnal types, but the quartan, which is comparatively a rare infection, is not so often seen with a coexisting malaria of other types.

The various complications that may occur in conjunction with malaria have already been discussed, and that these complications will result in variations of the clinical picture, depending on the particular symptoms of the complication, will be easily understood and will not be discussed at length.

It is plainly evident that a clinical diagnosis of malaria is far from satisfactory except under the most typical conditions, and when it is taken into consideration that in a very large majority of cases an absolutely positive diagnosis can be secured in a few moments of time devoted to the examination of the blood of these patients, it is certainly very poor practice to depend on anything else or to fail to make such an examination.

LABORATORY DIAGNOSIS.

For the purpose of examining blood for the detection of malarial plasmodia, it is useless to try to work with a lower power than a 1-12 oil-immersion lens; this should be combined with an 8X eyepiece. The microscope should be provided with a diaphragm and condenser, and while a mechanical stage is not absolutely necessary, it very greatly facilitates the examination of a slide. It is important that the student thoroughly familiarize himself with the picture of normal blood before relying on his examination of suspected malarial blood.

The examination of unstained blood for diagnostic purposes is not to be recommended; the small ring forms of the estivo-autumnal types are especially hard to detect in the unstained preparation, while the staining of a slide, after which it can be examined at any time, takes but a few moments, and greatly facilitates the detection of plasmodia. It is well, however, that the student work with unstained blood for the purpose of studying the morphological changes occurring in the various plasmodia.

In preparing a specimen of fresh blood for examination, a small drop should be placed on a thin cover-glass, everted, and immediately placed on a slide. Care must be taken that the drop be not too large, as it should be small enough to allow the corpuscles to spread out in a single layer, and not so large as to allow the formation of clumps or rouleaux, for such a preparation is worthless. The treatment of fresh blood for the purpose of demonstrating the flagellate bodies has already been described, and a detailed description of the morphology of the different parasites has been given in considering the classification of the parasites; it is therefore not necessary to describe them here.

While in the great majority of cases with active clinical manifestations, a few minutes examination will suffice to demonstrate the plasmodia, a smear should not be pronounced negative, unless examined for at least twenty minutes, and the time of examination, that will be most likely to demonstrate the plasmodia, is a matter that should receive careful consideration. The most likely time for a physician to be called to see a case of malaria is during, or soon after, the chill. At such times an examination of the blood for the detection of plasmodia is apt to be a long and tedious one, while a smear taken some hours later would demonstrate them in

a very much shorter time. Thayer considers that the best time to look for the parasites is eight hours before or after the chill. The author has found that any time six or seven hours after an exacerbation, and up to within four or five hours of the succeeding paroxysm, will usually demonstrate them, whereas immediately following, and for a few hours preceding a paroxysm, they are difficult to find; the schizonts can frequently be seen numerous in the peripheral circulation and gradually assuming advanced stages of development, only to disappear, suddenly, a few hours before sporulation.

There are many objects in both the stained and unstained preparations that may to the untrained eye be mistaken for plasmodia. In unstained preparations, particles of dirt, that remain on the slide, may under an improper focus apparently be surrounded with what appears to be a protoplasm, and be mistaken for small ring forms. Small granules from broken-down leucocytes resting on a blood corpuscle are often mistaken for plasmodia, but they, of course, possess no ameboid action, which is sufficient to differentiate them from the parasite. Small vacuoles within the red corpuscle are very deceiving, but with a proper focus the greater refraction of the vacuole will serve to distinguish it from plasmodia, its edges being well defined, while the edges of the parasite taper off as it were into the body of the red cell. Various causes may result in retraction of the hemoglobin leaving areas devoid of this blood constituent, resulting in a picture which may also be mistaken for plasmodia. Lack of ameboid movement with increased refraction should suffice to differentiate them.

In the stained preparation, blood platelets are the most common objects mistaken for plasmodia. Their smaller size, the absence of pigment, with the chromatin granules, if present at all, very much finer than in the plasmodia, together with the absence of a blue-stained protoplasm, are the points that serve to differentiate them. Blood-dust is also very often mistaken for the young hyaline forms.

From the above summary of some of the objects most frequently mistaken for malarial plasmodia, it will be seen that there are many pitfalls for the inexperienced observer, and there is little doubt that many get discouraged with their early attempts to establish malarial diagnosis by laboratory methods. Deaderick in discussing this point writes: "Most students gain the impression that all that is necessary to find the parasites is to locate a malarial subject

with any form of the disease and obtain the necessary blood at any stage of parasitic development, to stain it properly, and to inspect it under a high-power lens. Usually this is what he has been taught by textbooks and by teachers, and when he fails to detect the characteristic organisms in undoubted cases of malaria he is disgusted. The results of such teaching throw discredit upon a discovery whose practical importance is unsurpassed in modern medicine.'' It should be remembered that very often the stained specimens that have been seen by medical students during laboratory courses in college have been chosen from exceptionally rich infections, and that in actual practice cases in which blood is found containing such a profusion of parasites may be of comparative rare occurrence. At the same time we are confident that anyone wishing to familiarize himself with the various species of parasites and with their different stages of development will have but little difficulty if they are persistent, and give attention to detail in the preparation of their smears. After a few cases have been diagnosed positively with the microscope, and the parasites recognized beyond any doubt, the satisfaction is such, that one soon becomes dissatisfied with anything but a laboratory diagnosis, if it is possible to make it.

In addition to the presence of plasmodia in arriving at a laboratory diagnosis, the presence of pigmented leucocytes are of considerable significance. This pigment (melanin) is also often seen free in the blood-plasma; but the difficulty of differentiating it from particles of dust is such that it has little, if any, diagnostic value except when seen in the leucocytes. Craig writes, ''when, however, the pigment is observed enclosed in mono- or polynuclear leucocytes; when it is of a characteristic golden-brown or blackish color; and when several pigmented leucocytes are observed in two or more smears, carefully prepared, we are justified in making a diagnosis of malarial infection, either past or present.'' This last statement is one that should not be passed lightly. Just as the mere presence of malarial plasmodia may not mean malarial infection to the exclusion of all other pathological conditions, the presence of pigmented leucocytes may simply be evidence of a malarial infection ''past or present,'' and may not necessarily be a factor in the existing illness. It is therefore not safe to depend too strongly on the presence of pigmented leucocytes, in establishing a diagnosis of malaria, without ascertaining beyond all reasonable doubt that some coexisting pathological condition is not also present.

With the stained slide, in looking for plasmodia, it is well at the same time to count and record the leucocytes, securing a differential count, the significance of which has been dwelt on in considering the pathology of the disease. A total leucocyte count for the purpose of determining whether or not a leucopenia is present will serve as an auxiliary in making a laboratory diagnosis, and still another link in the chain may be secured by using the color index to determine the percentage of hemoglobin.

To summarize, in arriving at a malarial diagnosis by laboratory methods, we are assisted by: (1) the detection of plasmodia, (2)

Fig. 22.—Preparation of blood smear, the size of blood drop, and angle at which slide is held.

pigmented leucocytes, (3) a differential leucocyte count, (4) an absolute count, and (5) determining the percentage of hemoglobin.

In the preparation of a blood-smear we may choose from two methods: one, the thin film, in which the blood is spread out in a thin even smear, allowing the examination of each individual erythrocyte; the other, the thick-film method, in which a thick smear is made, in which, the hemoglobin being removed, the leucocytes, stromata of the red corpuscles, and the contained parasite, if present, are left for examination. The latter method has the advantage of allowing the examination of a much larger quantity of blood in a much shorter time than is permitted in the use of the thin film, but it also has its disadvantages, which will be dwelt on in the description of the method.

The Thin-Film Method.—A number of slides having been cleansed (and for this purpose there is nothing more satisfactory than washing them well with soap and water), the lobe of an ear, or a finger, is cleansed, dried, and punctured with a coarse needle. After rejecting a drop or so of blood, a small drop is placed on the slide by just touching it to the blood, not permitting the skin to come into contact with the glass. The specimen slide is now held between the thumb and finger of the left hand and at an angle of about forty-five degrees (Fig. 22), and the end of another slide (contact slide) held in the right hand is brought into contact with the blood drop, which will then be seen to flow by capillary attrac-

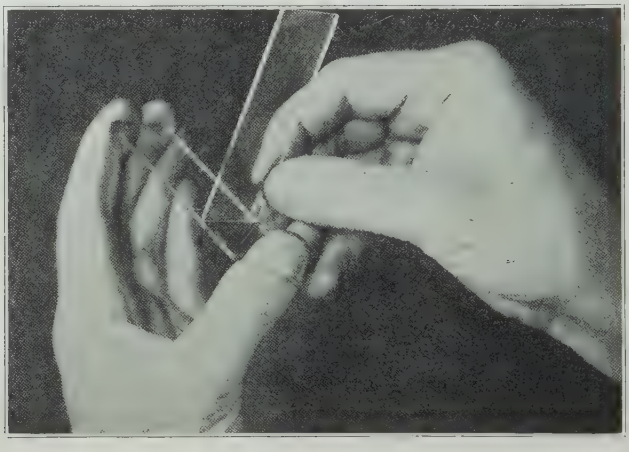

Fig. 23.—The contact slide, the blood running to the edges of the specimen slide by capillary attraction.

tion to the outer edges of the specimen slide (Fig. 23). The contact slide is now moved with a very light movement upward along the surface of the specimen slide, which will result in a thin even smear (Fig. 24), provided the slide is clean and free from oily substance. Scrupulous care in the cleansing of specimen slides and not allowing the skin to come in contact with the glass will avoid much trouble by eliminating particles of dust and débris from collecting on the specimen. While the beginner will possibly make many errors in the detection of the young hyaline ring forms, especially of the estivo-autumnal types, he will soon overcome this trouble, and with a little practice will soon learn to reject those small particles of blood-dust and débris, that, until properly focused

on, resemble or at least are often mistaken for the young malarial ring form. In fact, the picture of even the youngest hyaline ring form of an estivo-autumnal infection cannot be mistaken for anything else after familiarity with their staining qualities and morphological structure is acquired, which is done with a little practice. While films may be stained after they are many days old, the film of more than a few hours does not take the stain as well as the fresher preparation.

There are many methods of staining the malarial plasmodia. The author has used with universal success Wright's modification of the Leishman stain, which he has found a most

Fig. 24.—The contact slide having been passed rapidly upward over specimen slide, a thin even smear resulting.

satisfactory one for all blood work, while the malarial parasites are perfectly stained by properly observing the technic, which is moreover a most simple one, requiring but little practice to become perfectly familiar with. Certain objections to the use of this stain, as prepared under the original technic, have recently been overcome by a revised modification in the preparation of the staining fluid, which is given by Wright as follows:

To a 0.5 per cent aqueous solution of sodium bicarbonate add methylene blue (B.X. or "medicinally pure") in the proportion of 1 gram of the dye to each 100 cubic centimeters of the solution. Heat the mixture in a steam-sterilizer at 100° C. for one full hour, counting the time after the sterilizer has become thoroughly heated. The mixture is to be contained in a flask, or

flasks, of such size and shape that it forms a layer not more than 6 centimeters deep. After heating, allow the mixture to cool, placing the flask in cold water if desired, and then filter it to remove the precipitate which has been formed in it. It should, when cold, have a deep purple-red color, when viewed in a thin layer by transmitted yellowish artificial light. It does not show this color while warm. To each 100 cubic centimeters of the filtered mixture add 500 cubic centimeters of 0.1 per cent aqueous solution of "yellowish, water soluble" eosin, and mix thoroughly. Collect the abundant precipitate which immediately appears on a filter. When the precipitate is dry, dissolve it in methylic alcohol (Merck's reagent) in the proportion of 0.1 gram to 60 cubic centimeters of the alcohol. In order to facilitate solution, the precipitate is to be rubbed up with the alcohol in a porcelain dish, or mortar, with a spatula or pestle. This alcoholic solution of the precipitate is the staining fluid. It should be kept in a well-stoppered bottle because of the volatility of the alcohol. If it becomes too concentrated by evaporation and thus stains too deeply, or forms a precipitate on the blood-smear, the addition of a suitable quantity of methylic alcohol will quickly correct such faults. It does not undergo any spontaneous change other than that of concentration by evaporation, according to my personal experience. A most important fault encountered in the working of samples of this fluid is that it fails to stain the red corpuscles a yellow or orange color, but stains them a blue color which cannot be readily removed by washing with water. This fault I have recently discovered to be due to a peculiarity of the eosin employed. It can be eliminated by using a proper "yellowish, water soluble" eosin. Such an eosin I have obtained from R. L. Emerson, 739 Boylston St., Boston.

It requires not a little practice to properly prepare this stain, and if improperly done the resulting fluid is worthless. Those who have not the facilities or who do not wish to give the time necessary to acquire the technic can obtain the stain already prepared under the name of "Wright's Blood Stain" from any reputable physician's supply house.

The technic for the use of this stain is as follows:

Cover the slide with thirty or forty drops of the staining fluid or enough to thoroughly cover the preparation. At the end of a minute add the same amount of distilled water, allowing the solution to remain another two minutes or slightly longer if an intense coloring is desired. Now wash the slide in distilled water, for from a few seconds to a minute or so; this is an important step, and requires some practice to perfect. If the washing is continued too long, the blue staining of the protoplasm of the parasites, if present, becomes washed out, rendering their detection difficult. On the other hand, if the washing is not sufficient, the corpuscles will remain a bluish color, also rendering the detection of the parasites more difficult than when a proper differential staining is obtained. The time to cease the washing is when the film is just turning a pinkish or reddish-yellow color. If it is desired to pre-

serve the slide, it should not be mounted in an acid balsam, which results in the decolorization of the parasites in a short while. During the staining process it is well to place the slide on two parallel glass rods, which will have the effect of preventing all the fluid running off, if an excess happens to be placed on the slide; whereas, if it is allowed to rest on a flat surface, and the fluid once starts to run over the edge, most of it will drain off. After the slide is sufficiently washed, it is our custom to rapidly take up the remaining water on the slide with a smooth surface blotting paper, for the purpose of preventing a further decolorization. After examination, the slide, if to be preserved, should be carefully wiped off and placed in a suitable case that will insure its being kept free from dust accumulations.

Among other methods used for the staining of the plasmodia may be mentioned the Romanowsky, the Leishman, and the Nocht.

In the Romanowsky method two stock solutions are required. One consists of methylene blue (Grübler), 1 part, sodium carbonate, 1.5 part, distilled water, 100 parts; the other of a 1:1000 aqueous solution of "yellowish, water soluble" eosin.

For staining, 5 cubic centimeters of each solution are added to 95 cubic centimeters of distilled water; these two solutions are then mixed, using one part of the methylene-blue solution to two parts of the eosin solution. This stain is then applied to the film and allowed to remain for fifteen or twenty minutes, or longer, and then thoroughly washed in distilled water. This method is not so satisfactory as the Wright modification, the staining reactions being the same, but the technic requiring a much longer time.

The Leishman method calls for the preparation of the following staining solution:

Methylene blue	1	part
Sodium carbonate	0.5	part
Distilled water	100	parts

This solution is heated for twelve hours at 65° C., and then kept in room temperature for several days. At the end of this period a 1:1000 solution of "yellowish, water soluble" eosin is added to it, in equal parts, mixed, and allowed to stand for six to twelve hours. The precipitate which forms is then collected on a filter paper, washed with distilled water and dried, and .015 gram of the dried filtrate is dissolved in 100 cubic centimeters of methyl alcohol (Merck's reagent). The application of this staining fluid is similar in technic to Wright's stain, the smear being covered with the fluid for two minutes, distilled water added in about double the proportion of the stain used, the dilution being allowed to remain for about five minutes, when the film is washed in distilled water.

Ewing gives the following description of the Nocht method:

(1) To 1 ounce of polychrome methylene blue (Grübler) add 5 drops of 3 per cent solution of acetic acid (U.S.P., 33 per cent).

(2) Make a saturated (1 per cent) watery solution of methylene blue, preferably Ehrlich's rect. (Grübler), or Koch's, dissolving the dye by gentle

heat. This solution improves with age, and should be at least one week old.

(3) Make a 1 per cent solution in water of Grübler's aqueous eosin.

The mixture is prepared as follows:

To 10 cubic centimeters of water add 4 drops of the eosin solution, 6 drops of neutralized polychrome blue, and 2 drops of 1 per cent methylene blue, mixing well. The specimens, fixed in alcohol or by heat, are immersed for two hours, specimen side down, and will not overstain in 24 hours. The density of the blue stain may be varied to suit individual preferences. The above proportions need not be rigidly followed, but the polychrome solution should be accurately neutralized.

The Thick Film-Method.—Ross, in 1902, described a method for the detection of parasites in the blood by which one is enabled to examine a thick film of blood, instead of the method previously used in which a thin film is fixed and stained. His method consists of taking a large drop of blood scarcely spread out at all, and when dry, removing the hemoglobin by gently washing with water, and then staining the residual film. This results in the worker's being able to examine a very much larger amount of blood in a very much shorter period. The method does not seem to have come into general use in this country, and for which the author is unable to see the reason; for in many instances the advantages are so great that, once the technic is acquired, it will always be used in certain types of cases, where the parasites are few and difficult to find in the thin-film method. The relation of the parasite to the red corpuscle is of course destroyed, and one has to be familiar with the picture of the parasites to work with the method to advantage; but once the technic is mastered the saving of time is so great that one is well repaid for the time devoted in becoming familiar with the method. It is of especial value where there is reason to believe that, in spite of the absence of clinical symptoms, the infection has not been eradicated. In cases that have marked clinical symptoms and in which there has been no quinin administered in any form, there will usually be no difficulty in making a laboratory diagnosis with the thin film, but in those cases that have taken quinin, in some of the so-called "chill tonics," or in other forms, in doses insufficient to control the clinical manifestations, but sufficient to cause the majority of parasites in the peripheral blood to seek the deeper tissues, the thick film is especially valuable. Owing to the thickness of the residual film, after the hemoglobin is removed, the parasites appear in various irregular shapes, to an even more marked degree than in the other method.

The technic, originally suggested by Ross, has since been amplified and modified by Ruge, Bell, and Laing, and by James and the author in this country.

Ross' original technic is as follows:

A quantity of blood, say 1 cubic millimeter, is spread over only about ¼ square centimeter of area, and allowed to dry. The hemoglobin is then washed out with water, and the residue, consisting of parasites, leucids, micrids, and the stromata of the hematids, is stained by any appropriate method.

James was the first in this country to publish the results of work carried on under a modified process of his own, and the author published, a few weeks later, another modification which he had been perfecting for some time previous. James' modification is as follows:

A thick smear having been made as previously described, the slide is immersed in ethyl alcohol, which has been acidified by the addition of ten drops of commercial hydrochloric acid to 50 cubic centimeters of the alcohol. The slide is left in this solution until the hemoglobin is removed, which takes from ten to twenty minutes, depending on the thickness of the film. The slide is now washed in running tap water a sufficient time to remove all traces of the acid, this step taking from fifteen to twenty minutes. The smear is now ready for staining, which can be accomplished by any of the usual methods, taking well the Wright stain. It requires a little longer time to properly stain a thick film than is required in working with thin films, and the dilution must be greater when the water is added.

An objection to this technic is the time involved, although, if it is not desired to make immediate examination of the film, it may be left in the acidified alcohol and the process completed at the convenience of the examiner.

The following modification suggested by the author results in the saving of considerable time, and when the technic is carefully observed presents a pretty picture. It is as follows:

A thick smear having been made and allowed to dry, the slide is gently immersed in a 5 per cent solution of glacial acetic acid for from one-half to two minutes, depending on the thickness of the smear, or long enough to remove the hemoglobin, then washed in 95 per cent ethyl alcohol for a few seconds, rinsed in distilled water, covered with a 2 per cent solution of sodium bicarbonate for twenty seconds, washed in water, then in alcohol, and without drying, stained. For this purpose we have used Wright's, but as in the James' or any thick-film technic, in adding the water, it is necessary that the dilution be greater than is used when working with a thin smear. The entire process including the staining is completed in a little over five minutes. Only such ingredients as are chemically pure should be used, including in all

instances distilled water; and it is imperative that the acid should be neutralized, or the protoplasm of the parasites will not take the blue stain. It is also important that the alkali should not be in excess, or the film will take an intense stain from the methylene blue, which cannot be satisfactorily washed out without also decolorizing the parasites. Of course, in this method, as in all thick-film methods, the relation of the parasite to the corpuscle is lost, making the identification of the parasites more difficult to one not perfectly familiar with the picture. It should be stated that the acid solution results in a shrinkage of the protoplasm of the parasites, while the crescents of the estivo-autumnal infections, as a result of this action, appear very much smaller, but their general contour is in nowise affected, so that there is absolutely no difficulty in their recognition.

The importance of an examination of the blood in all malarial countries cannot be overestimated. There are so many other diseases having a more or less high rate of mortality, the clinical picture of which may resemble that of malaria, which may terminate in recovery if properly diagnosticated, but which, if treated for malaria, may run a very much longer and more serious course, or even terminate fatally, that it is of extreme importance that a diagnosis of malaria should not be made unless the infection is really present. On the other hand, it is of equal importance that all cases of malaria be classed and treated as such, not only for the period during which clinical symptoms are present, but also until all forms of the parasite are eradicated. On this account it is very necessary that, in every case where malaria is suspected, an examination of the blood should be made, and not only a single examination for the purpose of establishing a diagnosis; for the duty of the attending physician has only commenced when such a diagnosis is made, and he shirks one of the most important duties he owes to the community in which he lives, unless he keeps these patients under observation for several weeks, not discharging them until satisfied by repeated examinations of the blood that all forms of the plasmodia are eradicated. When malaria is treated in such a manner, then, and not until then, can we hope to see any great permanent reduction of the disease in those communities where it, while endemic, is not accompanied by a high mortality rate, or where the infections are not of great intensity. In districts where these latter conditions prevail, a combination of all the methods at our disposal for the prevention of the disease are apt to slowly become generally observed and followed out, and will gradually have to result in the reduction of the disease, but with the present at-

titude of the majority of general practitioners, the outlook for the eradication of malaria is far from encouraging. In considering the prophylaxis of the disease, much has been written on the education of the laity; to this propaganda should be added the education of the physician on the proper treatment of the disease, to a point where he will desist from the pernicious habit, which is a common one, of withdrawing treatment from a case of malaria just the moment that there is no clinical evidence of the infection.

DIFFERENTIAL DIAGNOSIS.

Typhoid Fever.—There is no difficulty in differentiating this disease from the tertian or quartan infections, but with the estivo-autumnal types, it is often impossible to make a differential diagnosis without the aid of the microscope. The use of the term typho-malaria has already been dwelt on. In 1898, during service with the Second Army Corps, in the Spanish-American War, the author saw hundreds of cases sent from his own and other regiments to the division hospitals, with diagnosis of malaria, and typho-malaria, practically all of which were afterward declared to be typhoid fever. Dock, who made an investigation of the prevalence of malaria in this corps, writes, "In the first division hospital I was told that there were a great many cases of malaria and typho-malaria. Several so-called typical cases of the latter had no parasites and were evidently uncomplicated cases of typhoid fever." Fully 50 per cent of the cases of typhoid fever occurring in our troops during the Spanish-American War were incorrectly diagnosticated, and the physicians who made these errors were certainly of as high a standard of efficiency as prevails among general practitioners in civil life. Of these cases incorrectly diagnosticated 90 per cent were attributed to malarial infections, and when it is considered that with our present laboratory methods a positive diagnosis can be secured in fully 95 per cent of both these fevers, it is very evident that we should not endanger the lives of such patients, by relying on a clinical diagnosis. The presence of the plasmodia and the absence of the Widal test will generally establish a malarial diagnosis. It must not be forgotten, however, that malarial plasmodia may be present during the first few days of a typhoid invasion, or during convalescence, and that the Widal reaction may not be secured until after the seventh day, and in some instances may not be present during any stage of the disease. Such

cases should receive antimalarial treatment, being carefully watched; and if after four or five days of vigorous treatment the fever is not under control, typhoid fever should be suspected, and the treatment governed accordingly. In those cases negative to the Widal reaction, and resistant to quinin, the diagnosis of typhoid, if present, can be established by a blood-culture. A valuable auxiliary test for the purpose of establishing a diagnosis of typhoid in undetermined cases of fever is the macroscopical agglutination test of Bass, and a differential leucocyte count will also be of assistance in determining between malaria and typhoid fever, a marked rise of mononuclears, accompanied by a leucopenia, being characteristic of malarial infection.

Dengue.—This disease may be confused with malaria unless a blood examination is made. Clinically, the prostration from dengue is more marked than in those forms of malaria with which it is likely to be confounded. Pain is a much more prominent symptom of dengue than of malaria and is more intense. The epidemicity of dengue will often be of help in determining a diagnosis, the rapidity with which the disease spreads, when once introduced, being very marked. Whole families will rapidly become ill, and from 50 to 75 per cent of the entire population may develop the disease in a remarkably short time.

Abscess of the Liver.—This, a common pathological condition in tropical countries, is often confounded with malaria, but as in other conditions, an examination of the blood will clear up the diagnosis. It should be remembered, however, that the plasmodia often coexist with this pathological condition, and care must be taken in the significance attributed to their presence. As it is a common sequela to specific and amebic dysentery, these diseases, often complicated with malarial infection, make it imperative that, in suspected cases of abscess of the liver, too much importance be not given the mere presence of plasmodia. Pain and tenderness over the liver region, with enlargement of this organ, and absence of splenomegalia, differentiate the diseases clinically, but in old malarial subjects there may, however, also be an enlargement of the spleen.

Cholecystitis.—The author has often seen this condition mistaken for malaria. There may be a periodicity in the chills, resembling a double tertian or a quotidian infection. An examination for the plasmodia, and a differential blood-count will clear up the diagnosis. In cholecystitis there will be a leucocytosis, with a large relative

increase of the polynuclears, which is not the blood picture in a malarial infection.

Appendicitis.—The author recently reported a case of benign tertian malaria with very marked symptoms of appendicitis. An initial chill, followed by a temperature of 99.2° F., with intense pain over the region of the appendix, vomiting, and a marked rigidity of the right rectus, caused a tentative diagnosis of appendicular colic. The following day the condition had very much improved, and the patient was comparatively comfortable, but forty-eight hours from the initial symptoms, a chill, with all the previous accompanying symptoms intensified, and a temperature of 106° F., which fell in a few hours to nearly normal, caused him to suspect malaria, at least as a complication. An examination of the blood revealed the tertian plasmodia in large numbers; antimalarial treatment was followed by a complete cessation of all abdominal symptoms, and the patient went on to a rapid recovery. Other similar cases have been reported. Appendicitis can be differentiated from malaria, by the absence of plasmodia in the blood, and a marked leucocytosis, with great excess of polynuclears. Too much attention should not be paid to pain in the belly, as it is often a prominent symptom in malaria, as well as in appendicitis.

Yellow Fever.—Where this infection is suspected, especially important is the examination of the blood for plasmodia, by which means only, in many mild cases, can a differential diagnosis be secured. While in severe cases of yellow fever distinctions are marked, in atypical cases there is a great similarity to the bilious remittent type of malaria. Albumin in the urine, present early in yellow fever, is not often seen in malaria until the infection has persisted for at least several days. The spleen is not enlarged in yellow fever, but in patients who have been more or less chronic sufferers with malaria, splenomegalia may be present. In yellow fever, a blood examination will show the absence of any increase of the large mononuclears, always present in a malarial infection.

Tuberculosis.—This disease is often confounded with chronic malaria. The clinical picture that these unfortunates present is in many instances very similar in either infection. In pulmonary lesions, the examination of the sputum will generally demonstrate the *Bacillus tuberculosis;* the blood picture is usually that of a lymphocytosis, the lymphocytes being in great excess, the plasmodia being absent. Physical examination will disclose the physical signs

present in a pulmonary tuberculosis, and as the disease advances, both these and the subjective symptoms render the diagnosis an easy matter. It is important, however, that a differential diagnosis be reached early in such infections, for many cases of tuberculosis, treated some months for a chronic malaria, and nothing else, may result fatally; whereas, if a diagnosis had been reached early in the disease, the prognosis might be affected. Contrary to former opinion, as has already been stated, the two diseases may coexist.

Kala Azar.—For a long time, and until recently, this disease was considered as nothing but a manifestation of malaria. It has now, however, been established as a disease *per se,* and the specific cause, the Leishman-Donovan bodies, has been isolated. The characteristic symptoms of this disease—an irregular fever, enlarged spleen, anemia, with more or less marked prostration—are such as to make almost impossible a differential diagnosis, where the two diseases are known to exist, without an examination of the blood. Quinin is said to have no effect on the clinical course of kala azar.

Dysentery.—The common coexistence of this disease with malaria makes it very hard, in some instances, to definitely determine the significance of plasmodia when they are found in cases of fever having symptoms of a dysentery. Where the dysenteric symptoms are due to specific or amebic origin, an examination of the feces will suffice to establish the diagnosis, by the finding of *B. dysentericæ,* or amebæ. It is therefore imperative, in trying to arrive at the etiology of a dysentery, in countries where all of these infective agencies are present, that a careful microscopical examination be made, not only of the blood of these patients, but also of their feces.

Sunstroke.—The known effect of exposure to the sun in tropical countries on latent infections, causing them to assume an active state, and the fact that in the estivo-autumnal types of malaria such activity may be accompanied by pernicious symptoms, often make it hard to differentiate between such an attack and sunstroke. An examination of the blood in such cases is generally sufficient to clear up any doubt. Craig speaks of three cases that he saw brought into hospitals, supposed to be suffering from sunstroke, which on examination of the blood showed numerous plasmodia, establishing a diagnosis of malaria.

Septic Infections.—The similarity of the clinical pictures of malaria and puerperal sepsis has been already mentioned. Any septic or pyemic infection may simulate malaria. Thus pyelitis has often

been overlooked, and the disturbance attributed to malaria. Ulcerative endocarditis may also simulate the infection. A blood examination in any of these instances is sufficient to establish a diagnosis. The presence or absence of plasmodia, a leucopenia with an increase in the large mononuclears indicate malaria; while a leucocytosis with increase of the polynuclears would suggest a septic condition.

A very important matter, upon which the author has frequently touched, but which he wishes to emphasize, is the significance of plasmodia in the blood, in so far as other pathological conditions are concerned. It matters not under what circumstances the plasmodia are found, their presence is positive evidence of malarial infection. It is very necessary, however, to determine if their presence is the sole cause, or is even a factor in an existing illness. The finding of plasmodia in the blood often results in there being no further search made for other existing disease, where, as a matter of fact, the plasmodia, while possibly being a factor in the clinical picture, are not alone responsible for the production of the symptoms for which the patient has sought relief.

In regard to the relative frequency of the different infections, it may generally be stated that the benign tertian is as a rule the most frequently seen in both temperate and tropical countries. In certain sections of the tropics the estivo-autumnal types will be more often encountered, while the quartan is a comparatively rare infection in almost all localities. Of 2,803 cases of malaria observed by Craig, in soldiers returning from the Philippine Islands and from Cuba, 839 suffered from tertian malaria, 220 being double infections. The relative infrequency of the quartan type is shown by the same writer, who states that in 5,000 cases in which the plasmodia, in some form, were demonstrated there occurred only 26 quartan infections. In something over five hundred cases observed by the author in Florida during the past three years, but two cases of quartan malaria were encountered, and in several hundred observed in the Philippine Islands during the years 1900–1901, but three or four cases of this type are recalled. Of the estivo-autumnal types, the tertian is more frequent than the quotidian. Of 1,662 estivo-autumnal infections personally observed by Craig in the Philippine Islands, 1,473 were tertians. The report of the Department of Sanitation of the Isthmian Canal Commission for the year 1911 shows that there were 5,421 discharges and 25 deaths from estivo-autumnal infections; 836 discharges and no deaths from benign ter-

tian infections; and 72 discharges and no deaths from quartan infections.

SYMPTOMATOLOGY.

Tertian Malaria.—The symptoms of a single uncomplicated tertian infection are peculiarly characteristic. Exacerbations occur every forty-eight hours, at the time of the sporulation of the invading organism, the *Plasmodium vivax*. The clinical symptoms of the disease may be divided into three distinct stages: (1) the stage of chill; (2) the stage of fever; and (3) the sweating stage, during which there is a decline of the fever and a comparative feeling of comfort comes over the patient.

Stage of Chill.—The chill may for some days be preceded by a prodromal stage, in which loss of appetite, a general feeling of malaise, headache, and more or less aching of the bones are present. With its initiation the patient complains of coldness of the extremities, followed by a feeling of chilliness running up and down the spine; this later involves the entire body, and the patient shivers with cold. The lips appear blue, the general appearance being one of cyanosis, and the patient goes into a rigor, sometimes so severe as to shake the bed. While the chill, which lasts from a few minutes to an hour, seldom longer, is still on, the temperature commences to go up, and in many cases reaches 104° F., or even higher; nausea is generally present, and vomiting may occur; the pupils are generally dilated; the pulse of small volume and very rapid. The foregoing is a description of a typical tertian rigor, but it should be remembered that many cases will be encountered in which sporulation is accompanied by less marked symptoms, the patient simply complaining of slight, creepy chilly sensations, with slight headache, and unaccompanied by excessive high temperature.

In young children the initial symptom may be a convulsion. The author has known children playing around, apparently perfectly well, to be seized with convulsions, causing great alarm to the parents.

Stage of Fever.—While fever is present during the chill, the patient is unconscious of it, and the surface of the body appears cold. This is now rapidly succeeded by the hot stage, in which the patient experiences an alternate feeling, of discomfort from excessive heat, and a return of the chilly feeling. These sensations may alternate for an hour or more, when the chilliness entirely disappears, and the

patient becomes extremely uncomfortable, complaining of intense fever. The pulse now becomes full, sometimes dicrotic, and remains very rapid. The face becomes congested, having an apoplectic appearance, the conjunctivæ are usually injected, the respirations are rapid, and a bronchial cough is very often present. The discomfort of the patient increases, and he feels very ill; vertigo may be complained of, the headache is most severe, and pains in all parts of the body are complained of, being particularly severe in the back. The patient becomes very restless and at this time delirium is frequently present. The temperature may reach 105° F. or 106° F. Herpes is quite common, appearing on the lips or around the nose. This stage usually lasts four or five hours; it may be prolonged beyond this time or occasionally be of shorter duration.

Sweating Stage.—As the fever commences to subside, the patient breaks out into a perspiration, which is accompanied by a general relief from the disagreeable symptoms and discomforts of the preceding stages. The perspiration is sometimes very profuse, the coverings and bed becoming drenched. The temperature now falls rapidly, and the patient becomes, as a rule, very comfortable. With the disappearance of the fever, the headache and other pains complained of subside; the patient may fall into a sound sleep, and within three or four hours the temperature has usually become normal. With the sweating stage over, the patient may feel perfectly well in a few hours, and the following day is often ready to assume general routine duties. There may, however, remain a feeling of lassitude, and a slight headache.

The entire period from the initial chill to the abatement of symptoms occupies as a rule from ten to twelve hours. As before stated, it should be remembered that there may be very many variations in the clinical picture, and the symptoms accompanying sporulation may be very slight, in some cases not sufficient to place the patient in bed; in fact, the intensity of the symptoms is governed by the intensity of the infections, and the resistance offered by the infected individual. Sporulation occurs every forty-eight hours from the time the sporozoite is injected by the mosquito, but clinical symptoms occur only when sporulation has resulted in the formation of a sufficient number of merozoites to overcome the resistance of nature's forces.

If treatment is not instituted, in about thirty-six hours from the subsidence of clinical symptoms, or forty-eight hours from the time

the chill appears, another rigor takes place, followed by the same train of symptoms. Although sporulation usually occurs with regularity, paroxysms sometimes occur a few hours before the expected time. In such cases the attack is referred to as an "anticipating one"; while in those cases in which sporulation of the plasmodia is prolonged, either by improper treatment, or by other conditions, the attack is said to be "retarded." Following the completion of a single cycle, the spleen, often very tender, is generally enlarged, and practically always is after two or more cycles are completed. After the infection has persisted for a few days, from 25 to 40 per cent of cases will show traces of albumin in the urine, but this, as a rule, does not persist much beyond the period in which clinical symptoms are manifest.

Quartan Malaria.—The symptoms of a quartan infection, in a general way, simulate those of a benign tertian, except that, sporulation occurring only every 72 hours, exacerbations take place every fourth day. The prostration during the second stage may exceed even that seen in the benign tertian, and pernicious symptoms may intervene at any time. The period occupied by the entire three stages is of from eight to ten hours' duration. While a single uncomplicated infection with this type of parasite gives a peculiarly typical picture, it should be borne in mind that double or triple infections necessarily alter the picture, and while the latter are comparatively rare, double infections are not at all uncommon. Physical examination of a patient suffering from a quartan infection presents the same signs as those seen in a benign tertian.

ESTIVO-AUTUMNAL INFECTIONS.

Tertian Form.—While sporulation of this type of parasite involves the same length of time as does the parasite of the benign tertian, there are decided variations in the clinical pictures of the two infections. The prodromal symptoms are, as a rule, more marked than the benign form; loss of appetite, severe pains in the back and legs, with a dull heavy headache, accompanied by an extremely restless, nervous condition, characterize the prodroma. The gastric disturbance is more pronounced, and vomiting is often very severe. There may be no distinct chill; in fact, this is not, as a rule, very pronounced. The patient is likely to complain of a mere chilliness; the headache and pains throughout the body, especially in the back, become more severe, there is often an expression of fear

over the countenance, and the general nervousness of the patient is very pronounced. He has the feeling of impending disaster, the pulse becomes more frequent and is very weak. The patient feels much prostrated. Respirations become increased, and the temperature commences to go up, reaching 102° or 103° F. The high temperatures of the benign tertian are not so frequent in the estivo-autumnal types, except in those cases that take on pernicious symptoms. The stage of chilliness lasts from ten minutes to half an hour, seldom longer.

As the chilliness disappears the patient commences to feel the effect of the high temperature. He becomes very miserable, with a severe headache, pains in his back, and throughout his body, these symptoms often being accompanied by severe abdominal pain, suggesting the necessity of surgical intervention for appendicitis or cholecystitis, unless the diagnosis is established. The prostration at this period may be very intense, the pupils are usually dilated, and the face flushed. Polyuria is generally present, the urine often contains albumin, and microscopical examination will often show the presence of hyaline and granular casts. This stage is of much longer duration than the similar stage of the other malarial infections, lasting from eighteen to twenty hours, sometimes even longer.

The sweating stage is less pronounced than that in the benign tertian or quartan types, there never being the intense perspiration so often seen in the other infections. The skin is simply moist, and a general mild perspiration may be noticed. The temperature, which had commenced to decline toward the end of the second stage, now becomes normal, and in many cases subnormal. This stage also lasts longer than does the similar stage of a benign tertian or a quartan infection, the three stages usually covering a period of from thirty to thirty-six hours. The maximum temperature during the fever period is usually 103° or 104° F., seldom higher. Its course is apt to be more or less irregular, and does not undergo the steady decline seen in the benign tertian form. The fact that there is often but a few hours between the subsidence of one paroxysm and the succeeding one, has created the impression among a great many practitioners that the fever in a tertian estivo-autumnal infection is of a remittent character. In uncomplicated single infections, if carefully noted, the temperature curve will show a decided intermission, while a double infection with this type of parasite is apt to produce a continued fever, with an oscillating curve. The above symptom-

atology of an estivo-autumnal tertian does not include those cases which develop pernicious symptoms, which will be considered by themselves later.

Quotidian Form.—This type, produced by infection with the *Plasmodium falciparum quotidianum,* presents clinical exacerbations every twenty-four hours, concomitant with the sporulation of the parasite. The chill is more distinct than in the type previously described, and there is often a decided rigor. It is not, however, quite so pronounced as in the benign tertian. The rise in temperature is marked, and rapidly reaches its maximum, which is usually in the neighborhood of 103° F. The drop, which commences usually within four or five hours from the initial symptoms, is pronounced, sweating is quite profuse, and the entire three stages usually occupy not more than ten hours. The other clinical symptoms of headache, pains in the back and extremities, and general prostration, are the same in both types of estivo-autumnal disease.

PERNICIOUS FEVERS.

Pernicious malaria is not a disease *per se,* but may occur in cases developing an intense intoxication. On account of the fact that it is commonly seen in the estivo-autumnal infections, it has been considered by some as forming a special classification associated with the estivo-autumnal types. This is incorrect, for, while nearly all cases of pernicious malaria are associated with estivo-autumnal infections, cases of any type of malaria may develop pernicious forms, rarely being seen in the benign tertian and seldom in the quartan. It is not uncommon to see a patient apparently doing well during an attack of estivo-autumnal fever, when, without warning, serious symptoms may develop. The author recalls a case in his private practice some months ago, in which a young girl, fourteen years of age, had been ill with an estivo-autumnal tertian infection for nearly a week. Previous to his being called, she had been indifferently treated, but the first time he saw her, there was nothing in her condition to cause any alarm. At 8 o'clock in the morning her clinical picture was that of a moderate infection. She had a temperature of 101° F., and felt fairly comfortable, being in no great pain. At 2 o'clock the same afternoon, the author was hurriedly sent for, and on reaching the bedside found the child in tonic convulsions. She lapsed into coma in a short time, and in spite of all therapeutic measures, was dead in less than three hours. Many such cases are

reported in the literature, and should serve to warn all practitioners living in sections where these types may be encountered to be ever alert and ready for danger signals. We will therefore consider pernicious fevers under the head of symptomatology, as the different types seen really are the symptom-pictures that may be observed in any case of malaria taking on pernicious symptoms.

The author agrees with Thayer, who states that pernicious symptoms rarely if ever appear with the initial paroxysm of original infections, and that they are the result of neglected treatment. This must not be interpreted to mean that pernicious symptoms may not be primary ones in recurring cases, for, as a matter of fact, they often are, but that such symptoms do not develop early in original infections. The responsibility of the treatment of original infections is here again emphasized. It is in those cases that receive treatment during the clinical course of the disease, only to have it withdrawn at the end of a few days or a week, that are apt at any time to develop pernicious attacks, which would not occur if the treatment had been carried on a sufficient time to entirely eradicate the infection. The author has seen several cases of pernicious malaria in which young children, who appeared to be perfectly well, were stricken down while at play, and recalls two instances in which death occurred within twenty-four hours from the onset of the disease, in spite of the fact that treatment was instituted within a few hours of the initial symptoms. All of these cases gave histories of previous recent infections, and when it is taken into consideration that these young lives would not have been blotted out if their original illness with malaria had received appropriate treatment, the full significance of this carelessness is impressed upon us.

Factors in the production of pernicious symptoms are exposure, alcoholism, intercurrent disease, or any condition that results in the lowered resistance of the individual. It may generally be stated that pernicious symptoms develop as a result of an intense toxemia, generated by excessively large numbers of plasmodia, and governed by the individual susceptibility, natural resistance, or previous condition of the patient. The plasmodia may not appear in great profusion in the peripheral circulation, in fact, may sometimes be hard to find at all, but smears secured by spleen puncture will show large numbers in different stages of development.

The chief pernicious types of the disease are the comatose, eclamptic, algid, choleriform, pneumonic, and the bilious remittent.

Comotose Type.—Coma does not generally occur in original infections until after the patient has had several paroxysms, but when appearing in the course of a recurring infection, it may be a primary symptom. It may develop gradually, or the patient may be stricken down suddenly as in apoplexy; and in the latter form the most energetic measures are necessary to save the patient from death, which may occur within a few hours. In all cases developing symptoms of coma, in malarial countries, the blood should be examined at once for plasmodia, as a routine measure, a procedure which will save many cases that without a proper examination would be classified as apoplexy or sunstroke. In apoplectic seizures the blood is often the only index of the disease. The temperature generally reaches about 103° F., seldom becomes higher, the face congested, respiration rapid, the pulse of high frequency, small volume, and irregular. In cases developing coma gradually, there are no especial symptoms other than those seen in an ordinary attack; the patient is gradually overwhelmed with the toxin, and there may for a time be slight delirium, which gives way to a complete coma. The respirations may now become stertorous, the pulse becomes thready, weak, and very irregular, and the temperature may now become high, reaching 105° or 106° F. The patient may regain consciousness after a few hours, and go on to recovery, or may after a short while lapse back into unconsciousness, when death usually occurs from collapse.

Eclamptic Type.—This is a common type in young children. They are seized with violent pain in the back of the head, vomiting, followed by eclamptic seizures, after which they lapse into a profound coma. The fever is usually high, 104° or 105° F., the pulse rapid and full, respirations hurried, and the skin hot and dry. If the case is not seen early and prompt treatment instituted, death, in the majority of instances, ensues within a few hours.

Algid Type.—This type may be seen as a primary symptom in recurring or repeated infections, but more often follows after several paroxysms have occurred. It is characterized by, and presents the picture of, a complete prostration that accompanies the invasion: the surface of the body is cold, a cold clammy perspiration is very profuse, and the patient appears in collapse. The face is drawn, the eyes sunken, the voice feeble, the radial pulse may be imperceptible, cyanosis is usually present, and the respirations are feeble and rapid. The temperature is, as a rule, not high, and

in many instances will be subnormal. It is the most severe and dangerous of the pernicious types, and in spite of all treatment death may take place within a few hours from the initial symptoms.

Choleriform Type.—In a certain number of malarial infections symptoms closely resembling those of Asiatic cholera may appear. The stools become very numerous, taking on the characteristic rice-water stool of cholera, and may be accompanied by blood. During the first few hours of the appearance of this complication the fever is usually high, but rapidly falls; the patient becomes extremely weak from loss of fluid, while suppression of urine may be complete. The skin becomes cold and clammy, and the patient appears cyanotic. Death takes place from collapse, where the infection is not recognized and properly treated, but when the case receives prompt attention, recovery is the rule. The diagnosis of this type may be extremely difficult, and in sections where cholera is prevalent, an examination of the blood is the only method by which a positive diagnosis of malarial infection can be made.

Pneumonic Type.—Pneumonia may be mistaken for this type of pernicious malaria, it being a very common complication. The pernicious type takes on symptoms of a lobar pneumonia. In it, the plasmodia become localized in the capillaries of the lungs, resulting in a symptom-complex, closely resembling that of a pneumonic infection. Pain in the side, cough, and dyspnea are present. A moderately severe malarial infection may be running a typical course, when such symptoms develop and a pulmonary complication be suspected. While the physical signs of a pneumonia may be present, the temperature curve is unlike that seen in pneumonia, and with the subsidence of the malarial paroxysm, the pulmonary symptoms disappear spontaneously, possibly to return again with the next paroxysm. Careful observance of the clinical picture for twenty-four hours, or a little longer, together with an examination of the blood, will establish a diagnosis.

Bilious Remittent Type.—A peculiar type of pernicious malaria is that when the patient is seized with uncontrollable vomiting, jaundice is present, the patient extremely prostrated, and the case may be mistaken for yellow fever. In vomiting, large quantities of bile are ejected, the fever runs a high course, and is usually of a remittent type; the patient may become delirious, or coma may supervene. In such cases nothing but a blood examination will reveal the true nature of the infection. When treated, practi-

cally all of these cases will recover, but if neglected, death may occur.

Other Types.—There are many other pernicious types that may occur in malarial infections, such as the apoplectic, hemiplegic, typhoidal, tetanic, diaphoretic, cardialgic, aphasic, asthmatic, gastric, and rheumatic. They are comparatively rare, and will not be described separately. They take on the symptoms suggested by the applied terms, and as shown in the description of the various types of pernicious malaria just described, emphasize the fact that the only safe rule in all malarial countries is to make a routine practice of examining the blood of all cases in which there is any likelihood of the malarial plasmodia being a factor in the clinical symptoms, or in cases where it may be likely that the disease may be present in a latent or masked form.

CHAPTER VII.

LATENCY—RECURRENCES—CHRONICITY.

LATENT MALARIA.

The general subject of latent malarial infections as a predominating factor in the etiology of the disease is one that has been very generally overshadowed in the discussion of the other source of infection, the mosquito. Not only this, but the general view of the practitioner has been such in the treatment of the disease as to allow of the perpetuation of the infection in many places, where with proper treatment of such cases the disease would have rapidly disappeared. The author does not desire that anything in the following pages should be interpreted as the taking of any stand against mosquito extermination to the point of greatest possible reduction. All that he wishes to impress upon his readers is that we have in the past very much neglected *man* as a focus of infection. In discussing climatic conditions, favorable to the life span of the malarial parasites, it has already been shown that in many sections of the world, following the winter months, the infection has been eradicated by nature, in so far as the mosquitoes are concerned, and that, before they are again capable of producing the infection in man, it is necessary for them to feed on the blood of infected man—that is, blood containing the sexual forms of the parasite. This means that, if in a given community all latent malarial infections were cured in these winter months, mosquitoes could breed promiscuously, bite us freely, but that we should remain free of malarial infection. If, in addition to this, all imported cases, and those few that escaped observation, were properly treated just as soon as they were discovered, malaria would soon become a disease of the past.

It is a common occurrence to find plasmodia in the blood of patients suffering from other disease, and in that of those apparently well, and who appear to be suffering no inconvenience as a result of harboring the parasites. These are latent malaria carriers, and it is this class of cases that perpetuate the disease

in those sections where meteorological conditions are such as to destroy the parasites in the mosquito during the winter months, and is a most serious factor in any community considering a campaign against this disease. Absolutely responsible for the perpetuation of the disease in temperate climates, where the mosquito becomes free of infection during the winter months, the latent carrier also largely enters into the dissemination of it in even tropical countries, and it cannot be emphasized too strongly that the destruction of the plasmodia in these carriers is equally as important as is the destruction of the mosquito.

While such individuals may be apparently well, their hemoglobin index, and red corpuscle count, will always be below normal, and as a result of the pathological changes, brought about in acute attacks, which become more or less pronounced in the chronic carriers of the infection, their resistance becomes very much lowered. This results in all malarial countries having a higher mortality rate, exclusive of that directly due to malarial disease, than countries in which this disease is not present. The significance of malaria as a social factor is one that by a great many is not fully realized. Outside of the loss of labor resulting from malarial attacks, the actual earning power of individuals suffering from repeated attacks of malaria is very greatly decreased.

The presence of latent malaria has therefore a multiple significance: namely, lowered resistance, rendering such individuals susceptible to other disease; decreased earning power; and the provision of means for the perpetuation of the infection by the presence of sexual forms of the plasmodia, which will be taken up by the mosquito and undergo evolution whenever climatic conditions are favorable.

There has been comparatively little work done showing the percentage of latent carriers in malarial districts. Craig found 307 latent cases out of a total of 1,297 soldiers invalided home from the Philippine Islands. The same author cites the history of Company H, 16th United States Infantry, in which, upon returning from service in the Cagayan Valley, located in the upper end of the Province of Luzon, he demonstrated the plasmodia in 27 of 47 men doing duty, apparently well, and with no symptoms of malarial infection. Byrd has recently carried on some observations in the state of Florida, to determine the malarial index of

that state. The following table comprises the results of his investigations:

TABLE XIII.

Place.	White.				Colored.			
	No.	Pos.	Neg.	%	No.	Pos.	Neg.	%
Sarasota	60	2	58	3.5	16	6	10	37.5
Miami	117	6	111	5.1	0	0	0	
Little River	10	0	10	0.0	0	0	0	
Cocoanut Grove	10	0	10	0.0	0	0	0	
Fort Pierce	76	2	74	2.6	24	0	24	0.0
Oxford	45	3	42	6.6	0	0	0	
DeLand	55	5	50	9.1	45	5	40	11.1
Arcadia	31	0	31	0.0	0	0	0	
Gainesville	73	8	65	10.9	0	0	0	
Dade County	99	7	92	4.9	0	0	0	
Total	576	33	543	5.7	85	11	74	12.9

ETIOLOGY OF MALARIAL RECURRENCES.

Probably the most important point that is so far undetermined concerning our knowledge of malaria is the etiology of recurrences; in fact, it may be said that our knowledge of the disease and all that pertains to it is pretty complete with this single exception, and in reviewing the literature on this phase, one is impressed with the diametrically opposed views held by the various authorities, all of which are entitled to consideration.

The theories advanced in the past have not been many, and in recent years have been limited to the following:

(1) Parthenogenesis, or the reproduction of the organism by unfertilized macrogametes.

(2) Intracorpuscular conjugation, this being a process in which the young hyaline forms effect union with each other inside the corpuscle, resulting in a resting body, a resistant form capable of assuming a zygote stage, multiplying after periods of quiescence and only then giving clinical evidence of their presence.

(3) Asexual reproduction by schizogony, this reproduction taking place continually from the time of infection, and continuing after the subsidence of clinical symptoms, but then in numbers insufficient to produce clinical symptoms excepting under certain unknown conditions, when activity is resumed.

Parthenogenesis.—In 1903, Schaudinn advanced the theory that the macrogametes took on a parthenogenetic cycle—that is, were

able to multiply without fertilization by the microgametes—and attributed to this cycle recurring infections. Several other investigators had previously described sporulating gametes, but had not attributed to the cycle the significance that this author did, and while the theory may appear to be a reasonable one, it has not been generally accepted. Deaderick has subscribed to it, but offers no evidence in its support except to cite the case of Frau Kossel, reported by Schaudinn, in which it is claimed an alteration of the species was observed. Ross criticizes the deductions drawn from this case, calling attention to the fact that during the period that this patient was under observation the gametes varied in number, and that while there was a marked increase in their numbers the day before a paroxysm, considers that there was no evidence that they were not produced from ordinary spores, but that their variation in numbers itself suggests that they were being produced all the time, and that the source of asexual spores from which he considers that they were derived were too few to be detected by the method used. He calls attention to the fact that the cells were not actually observed in the process of development, but that it was inferred such development took place from a study of different cells in what was considered different stages of evolution. Deaderick, however, in following his line of argument in support of the theory, states that "these relapses at long intervals can be explained by parthenogenesis alone. After the schizonts have perished, while the microgametocytes do not persist long, the macrogametes remain for indefinite periods." In discussing a similar claim made by Schaudinn in the benign tertian infections, Craig does not confirm this statement in connection with estivo-autumnal infections, claiming that the male and female gametes remain in the blood for weeks after acute clinical evidence has passed away, and in practically the same ratio during the periods of observation. This has also been the author's experience in the estivo-autumnal infections seen in Florida.

In an address before the Liverpool School of Tropical Medicine, Ross stated that many of their cases suffering from relapses never showed any of the sexual forms, thus indicating that they are not a factor in this form of the disease. He and Thomson, in a series of cases, record, in several of them, a marked rise in the curve of sexual parasites, unaccompanied by any rise of temperature. In one case the gametes reached the high number of 1,500 per cubic

millimeter, remaining over a thousand for nine days, during which time there was no elevation of temperature, notwithstanding the fact that no antimalarial treatment was instituted. With these cases in mind, it is hard to associate recurring malarial infections with the theory of sporulating gametes. If such phenomenon resulted in recurrences, why is there no elevation of temperature in these cases showing a marked increase in the gametes and unhampered by treatment of any kind? To gather the full significance of this objection to the theory, we must recall the etiology of fever in malaria, which, as has already been stated, is due to the liberation of toxins at the time of sporulation, so that it is reasonable to infer that, if the sporulation of gametes, if such does occur, were a factor in recurrences, an increase of their numbers to any extent would be accompanied by an elevation of temperature. While it may be hard to reject what such an authority as Schaudinn reports as a positive finding, we cannot ignore the significant statement made by Thomson, that the phenomenon has never been observed by workers in the Liverpool School of Tropical Medicine, and "must be very rare, as it would otherwise have been noticed more often." If it is necessary to adduce further evidence that the sexual forms are not a factor in recurrent infections, it would seem that the question could be absolutely settled by inoculation experiments with blood containing only those forms. Ross cites four such experiments, one conducted by Thayer in 1898, and three by Elting in 1899. All of these were negative, three of them showing neither fever nor parasites at any time, while the other case had a slight rise of temperature two and six days after inoculation, but never showed any parasites. While these four cases may be considered as insufficient for final and conclusive laboratory evidence on which to reject the theory of parthenogenesis, they are of great significance, and together with the fact that Schaudinn's original deductions were based on a single case of benign tertian, and that all later evidence brought forward in support of the theory has been almost universally rejected, renders parthenogenetic forms (the very existence of which is a matter of great doubt) as being a factor in recurrences unlikely.

Intracorpuscular Conjugation.—The phenomenon of intracorpuscular conjugation of the young hyaline parasites was first observed by Mannaberg, and later described by Ewing. Neither

of these writers attributed to it the significance it deserves; and it was Craig who first described in detail the process of development and attributed to the resulting bodies the significance of their being a factor in recurrences, and he has since amplified the findings made in his original report by many additional contributions. The writer will not describe in detail this form of the evolution of the parasite in man, but will refer those interested to the many excellent contributions that the author of this theory has published.[1] Darling has confirmed the findings of Craig, saying, "the theories of Mannaberg and Craig explain the persistence of latent malaria by the process of conjugation of two ring forms within a red blood corpuscle." He also reports having frequently seen crescentic bodies in latent estivo-autumnal infections which he considered had been formed by the conjugation of two ring forms. While crescents and the sexual forms of the other types of the infection may be formed as a result of this process, we do not consider that these bodies have any significance in the etiology of recurrences, or that the sexual forms have any other function than the perpetuation of the species when transferred to the mosquito.

The author recently had under observation a case of considerable significance toward the verification of conjugating bodies. The patient had been unwell, complaining of a general malaise for some weeks, but showed no clinical symptoms; following routine procedure his blood was examined for plasmodia. Several smears at intervals covering a period of three weeks failed to reveal the parasite in any of its forms, but at the end of this time several parasites of a ring form, showing unusually large chromatin masses, with the protoplasm also larger than usual and staining an intense blue, were observed. The patient had never had malaria previously. He was at once put on 30 grains of quinin sulphate per diem, but contrary to the usual result, while the fever disappeared, the same organisms were present in the peripheral blood for several days and proved very resistant to treatment. The author did not observe forms in any advanced stage of development, but is satisfied that what he did see were the result of conjugation. Craig has stated that intracorpuscular conjuga-

[1] These have been many, but the author especially calls attention to the very excellent monograph published by Doctor Craig in the *Journal of Infectious Diseases*, Chicago, Vol. VII, No. 2, March 1, 1910, pp. 300–318, entitled "Studies in the Morphology of Malarial Plasmodia after the Administration of Quinin, and in Intracorpuscular Conjugation."

tion never occurs during the first few days of an acute malarial infection, and that on this account it is not seen in initial attacks. The case referred to would indicate that in persons possessing a relative immunity the process may take place even before clinical symptoms of the infection are present, and is still another reason why we should arrive at a diagnosis of these infections as early as possible.

While the different stages of development up to the form of what is considered by Craig to be the presporulating stage have been carefully studied by this author, we have as yet no laboratory evidence that these bodies result in recurrences, and while without such evidence it is impossible to absolutely fix their significance, we feel confident that they will be proved to be the factor in relapses of long interval.

Asexual Reproduction by Schizogony.—It has heretofore been thought that the asexual forms disappeared from the peripheral circulation in the long intervals between clinical manifestations of the infection. Ross and Thomson have shown that this is incorrect, and that the error was due to imperfect methods for their detection. In conducting some enumerative studies of the disease, by the application of the thick-film method, they show in a series of cases, by daily counts, that the asexual forms become less and less after an acute clinical manifestation of the disease, sometimes for a few days being zero, and from that to four or five per cubic millimeter, but in many of these cases, although for a few days the parasites cannot be detected, they then slowly increase, giving clinical evidence of their presence only after reaching some hundreds per cubic millimeter. With this demonstration arises the very important question: How long can schizogony continue without giving rise to clinical symptoms, and is it a factor in recurrences of long interval?

The almost universal opposition to the acceptance of this theory has been that it is unreasonable to infer that schizogony could go on for weeks, months, and sometimes for years, sufficiently to maintain the infection, but within such limits as to shut out clinical symptoms for long periods of time. Ross, who upholds this theory, which he says he "will continue to adopt until a better one is established," in replying to the argument that it is unreasonable to think that the asexual forms can multiply for long periods of time, without giving rise to symptoms, but sufficient to maintain

the infection, writes: "It is impossible to accept such a train of thought. If 150,000,000 sporids cause but a little fever in a man of medium weight, 1,000 or 100 should cause none at all, and yet will be quite sufficient to keep the infection alive in him. But if the parasites are so few, what chance has the medical man of finding a single one? If even 1,000 parasites are present in a man of 10 st. weight, the chances are that we must search 15,000,000 hematids before we find one parasite. At the rate of 10,000 hematids a minute, we shall have to search for 1,500,000 minutes, or for twelve hours a day for more than five years, before we succeed." These figures, to say the least, strikingly demonstrate the likelihood of negative findings in positive cases.

It is very evident that there is a factor, at present unknown, which is either responsible for the resumed activity of malarial plasmodia in man after periods of latency more or less prolonged, or checks activity for these periods. Is it possible that this factor is enough to prohibit the multiplication of the parasites to a number sufficient to produce clinical symptoms? May it not be the same factor, also as yet undetermined, that in untreated cases, by the production in the blood of some antitoxic substance, prevents the continued multiplication of the parasites to the point that would mean death in every instance?

A review of the literature of the etiology of recurrences, a brief resumé of which has been given, leads the author to conclude that:

(1) Parthenogenesis cannot be considered a factor in recurrences for the following reasons:

(a) The very existence of such a phenomenon is a matter of great doubt, many observers working over a period of years having failed to demonstrate such forms.

(b) There are many cases reported that have at no time during the infection shown the sexual forms, but have frequently relapsed.

(c) The four cases, cited by Ross, in which inoculation experiments contained only sexual forms, failed in each instance to produce clinical symptoms of malaria, or to reveal the presence of any plasmodia; while in 51 cases cited by the same author inoculation experiments containing the asexual parasites in every instance produced clinical symptoms of the infection, and parasites of the type inoculated were demonstrated in all of the cases experimented with since the discovery of the plasmodia.

(2) Intracorpuscular conjugation is not an occasional phenomenon, but is generally present in recurring cases. The observations of Craig that certain forms of the plasmodia exist only when conjugation is present, and often before gametes have appeared, would indicate that they are a factor in recurrences of long interval, and while they have only been followed by him to a presporulating stage, and further observations on their morphology are necessary to absolutely associate them with recurrences, there is good reason to believe that such studies will establish them as the etiological factor in long interval relapses.

(3) Asexual reproduction by schizogony is generally accepted as the cause of short interval relapses, but the length of time that the schizont is capable of keeping the infection alive in man without producing clinical symptoms is at present undetermined, and can be only determined by future laboratory observations on an extensive scale.

SIGNIFICANCE OF RECURRING INFECTIONS.

The significance of a recurring malarial infection is that it is *prima facie* evidence that the original infection did not receive appropriate treatment. This results in the patient, not only being a sufferer as a result of the infection a longer time than he would under proper treatment, but also being a constant menace to the community in which he may reside, provided that *Anophelines* are present, which in turn become infected from his blood-stream and transmit the disease to others. Just as long as the infection is present is there a possibility of the formation of gametes, and as already shown, every individual gamete carrier is of considerable significance in the perpetuation of the disease. The absence of relapsing cases would mean that all first infections were receiving proper treatment, the neglect of which at the present time is a leading factor in the present endemic index of the disease. Craig most truly states that "the practice of regarding such infections as cured because the active symptoms of the disease have disappeared is a most common and a most pernicious one, and one that is responsible for the transmission of a very large proportion of malarial disease." There is plenty of evidence showing that early and efficient treatment arrests the development of gametes, and while in exceptional cases conjugating forms, which are probably responsible for recurrences of long interval, may form early

in the disease, they generally do not form until late in the infection; so it is evident that, if these cases receive appropriate treatment early in the infection, gametes, resulting in the infection spreading to non-infected mosquitoes, will not form, and that conjugating bodies, which keep the infection latent in man for an indefinite period, causing a great deal of suffering, will likewise be arrested in development.

FREQUENCY OF RECURRENCES.

We think it may be stated that, with the present manner of treating malaria in most sections, practically every original infection is followed by one or more recurrences. It is a somewhat hard matter to classify recurrent infections, owing to the fact that in a great majority of instances it is practically impossible to exclude the possibilities of reinfection, in cases that may be suspected to be recurrences. Celli considers all cases showing clinical manifestations during the same year as being due to a single infection. It is, we think, impossible to accept such a classification, for there are undoubtedly many persons infected more than once during such a period. The author considers that many such reinfections will often be sufficient to precipitate an attack in individuals harboring the parasite in a latent form, which would not at the time become active were it not for the added infection, and again slight infections might not be sufficient of themselves to precipitate an attack, except in those that already harbor a certain number of parasites in a latent stage, at the time of this further infection. The presence of sexual forms in the blood during the first few days of clinical manifestation is evidence that the case is a recurring one, for these forms do not occur early in an original attack; the absence of sexual forms, however, does not prove that the case is an original infection, as in some cases none of these forms develop at any stage of the disease.

The following tables given by Craig, showing the time of recurrences in the estivo-autumnal tertian and in the benign tertian infections, are of interest. He states that they are prepared from carefully selected cases in which reinfections were extremely improbable:

TABLE XIV.

Recurrences in 55 cases of Tertian Estivo-Autumnal.

Case No.	Initial attack.	First recurrence.	Second recurrence.	Third recurrence.	Fourth recurrence.	Fifth recurrence.
1	Oct. 12	10 days	30 days	36 days	.....	.....
2	Nov. 19	12 days	.....	.....	.....	.....
3	Feb. 27	15 days	20 days	30 days	.....	.....
4	Nov. 2	18 days	30 days	30 days	.....	.....
5	Mar. 30	19 days	20 days	.....	.....	.....
6	Dec. 8	19 days	.....	.....	.....	.....
7	Jan. 24	20 days	.....	.....	.....	.....
8	Feb. 12	20 days	60 days	.....	.....	.....
9	Dec. 24	20 days	.....	.....	.....	.....
10	Feb. 6	20 days	20 days	.....	.....	.....
11	Feb. 6	20 days	48 days	.....	.....	.....
12	Dec. 25	21 days	33 days	.....	.....	.....
13	Mar. 1	22 days	.....	.....	.....	.....
14	Nov. 29	22 days	.....	.....	.....	.....
15	Nov. 14	24 days	.....	.....	.....	.....
16	Feb. 4	24 days	20 days	38 days	30 days	.....
17	Oct. 30	24 days	16 days	.....	.....	.....
18	Aug. 29	24 days	26 days	.....	.....	.....
19	Mar. 17	24 days	.....	.....	.....	.....
20	Feb. 4	25 days	16 days	20 days	.....	.....
21	Dec. 30	26 days	36 days	30 days	90 days	30 days
22	Jan. 26	26 days	48 days	90 days	.....	.....
23	Jan. 11	26 days	22 days	.....	.....	.....
24	Oct. 2	27 days	.....	.....	.....	.....
25	Nov. 2	27 days	.....	.....	.....	.....
26	Mar. 2	27 days	52 days	.....	.....	.....
27	Feb. 5	28 days	21 days	20 days	21 days	.....
28	Dec. 12	28 days	28 days	.....	.....	.....
29	Oct. 29	29 days	48 days	15 days	.....	.....
30	Jan. 17	30 days	.....	.....	.....	.....
31	Jan. 1	30 days	30 days	.....	.....	.....
32	Jan. 19	30 days	.....	.....	.....	.....
33	Jan. 20	32 days	.....	.....	.....	.....
34	Oct. 19	33 days	26 days	90 days	.....	.....
35	Jan. 19	34 days	40 days	.....	.....	.....
36	Oct. 18	34 days	50 days	.....	.....	.....
37	Jan. 25	34 days	26 days	17 days	.....	.....
38	Oct. 21	36 days	56 days	.....	.....	.....
39	Feb. 3	36 days	66 days	.....	.....	.....
40	Aug. 13	36 days	35 days	.....	.....	.....
41	Nov. 27	36 days	.....	.....	.....	.....
42	Sept. 1	37 days	49 days	.....	.....	.....
43	Oct. 18	38 days	.....	.....	.....	.....
44	Oct. 17	38 days	.....	.....	.....	.....
45	Aug. 13	38 days	.....	.....	.....	.....
46	Sept. 6	41 days	.....	.....	.....	.....
47	Oct. 31	42 days	20 days	.....	.....	.....
48	Jan. 1	45 days	30 days	.....	.....	.....
49	Nov. 3	46 days	21 days	.....	.....	.....
50	Dec. 7	49 days	.....	.....	.....	.....
51	Feb. 24	50 days	24 days	41 days	.....	.....
52	Oct. 24	51 days	39 days	.....	.....	.....
53	Jan. 18	61 days	156 days	.....	.....	.....
54	June 14	64 days	66 days	14 days	20 days	20 days
55	Mar. 3	80 days	120 days	96 days	.....	.....

TABLE XV.

Recurrences in 18 Cases of Tertian Malarial Infection.

Case No.	Initial attack.	First recurrence.	Second recurrence.	Third recurrence.	Fourth recurrence.	Fifth recurrence.
1	Nov. 2	16 days	21 days	.....	.....	.....
2	Aug. 4	18 days	20 days	.....	.....	.....
3	Aug. 28	19 days	30 days	26 days	46 days	.....
4	Nov. 6	20 days	24 days	.....	.....	.....
5	Jan. 17	20 days	32 days	30 days	24 days	.....
6	Nov. 23	21 days	20 days	26 days	.....	.....
7	Oct. 6	21 days	30 days	.....	.....	.....
8	Sept. 17	21 days	22 days	27 days	.....	.....
9	Aug. 27	22 days	36 days	.....	.....	.....
10	Feb. 12	22 days	18 days	16 days	27 days	.....
11	Jan. 17	27 days	.....	.....	.....	.....
12	July 20	30 days	.....	.....	.....	.....
13	May 3	30 days	.....	.....	.....	.....
14	Nov. 1	30 days	.....	.....	.....	.....
15	Sept. 22	33 days	.....	.....	.....	.....
16	Sept. 1	37 days	.....	.....	.....	.....
17	Dec. 13	38 days	.....	.....	.....	.....
18	Sept. 22	41 days	.....	.....	.....	.....

MASKED MALARIA.

The author has already dwelt on the necessity of ascertaining beyond any doubt just what significance should be paid to the finding of plasmodia in the blood, in so far as considering to what extent they are responsible for existing illness. Whenever they are demonstrated in the blood, it is evidence of malarial infection, but it need not necessarily mean malarial disease. By this we mean: a person presenting himself for examination and treatment, complaining of certain clinical evidence of other disease, whose blood upon examination shows the presence of plasmodia, who, while harboring the parasites, may not necessarily be suffering any inconvenience therefrom, is infected with malaria, but the condition for which he seeks relief is not malarial disease, and may have no bearing whatever on the pathological condition existing. Whenever, however, plasmodia are found, it is very necessary that the same efficient treatment accorded cases showing clinical symptoms be given such cases; but great care should be taken not to allow their finding to mask other disease, and it is also imperative that other diseases having symptoms in common with malaria should not be allowed to mask malarial disease. In cases where quinin has been administered before an examination of the blood is made, it may often be a hard matter to establish such a diagnosis. The only safe rule to adopt, therefore, in all malarial countries, is to be on the lookout for coincident malaria in any and all illnesses, and

the routine examination of the blood of all patients in such districts will often serve to establish a complete diagnosis, thereby hastening the convalescence of such individuals. Pulmonary tuberculosis, abscess of the liver, dysentery, either specific or amebic, typhoid fever, septic conditions, and gonorrhea may be mentioned as diseases occurring in malarial districts that frequently mask malaria.

CHRONIC MALARIAL CACHEXIA.

Individuals suffering from chronic malarial cachexia are seen more especially in those sections where the estivo-autumnal infections are present. Their clinical picture is one that can hardly be overlooked, and while it may be difficult to differentiate the condition from such diseases as kala azar, anemias secondary to other diseases, such as uncinariasis and chronic sepsis, in fact, any infection producing degenerative changes in the blood, a careful blood examination will clear up the diagnosis. Cases of chronic malarial cachexia nearly always present a very much enlarged spleen, and there is always marked evidence of anemia, with a history of irregular exacerbations of fever. Nephritis is often present, and any of the pathological changes that have been described as occurring in the disease may be more or less marked. An examination of the blood will reveal a low red-corpuscle count, a decrease in the hemoglobin, a leucopenia with marked increase of the large mononuclears, diminished eosinophiles, and the presence of parasites. The last may not be present in the peripheral blood in any great numbers, especially during the period between active fever manifestations, but on splenic puncture, or in the deep tissues at post mortem, especially the bone marrow, the plasmodia are very numerous.

CHAPTER VIII.

PROPHYLAXIS.

It has been definitely established that the necessary factors for the production of malaria are: the presence of malaria-carrying mosquitoes, and sexual forms of the parasite in the blood of man. With these two factors present, if opportunity is given the mosquito to bite man, malaria will become endemic, more or less, depending on the number of mosquitoes present capable of transmitting the infection, and the number of individuals harboring the sexual forms of the plasmodia in their peripheral circulation, and only under these conditions can the disease remain endemic.

The control and prevention of malaria may be considered under the following headings:

(1) Measures directed against the plasmodia.

(2) Measures directed against the mosquito.

(3) Mechanical means to prevent the mosquito from gaining access to man.

(4) The education of the public on all measures for the control and prevention of the disease.

MEASURES DIRECTED AGAINST THE PLASMODIA.

Measures directed against the plasmodia consist of the interference with the evolution of the parasite in infected man, by medication, for the purpose of preventing the formation of gametes and the destruction of those that succeed in forming in the blood.

It is generally conceded, and has been abundantly demonstrated by laboratory observation, that gametes do not form during the first few days of an original malarial invasion. We have already discussed the formation of gametes in the blood of man, which takes place as a result of the action of the human host on the young merozoites after sporulation has gone on for some time. On this account gametes are not seen in a tertian infection until the disease has been dominant for at least a week, while in the quartan and estivo-autumnal infections they are not encountered before the

eleventh day. It is therefore very evident that, if appropriate treatment is instituted early, and carried on a sufficient time to insure the complete eradication of the parasites in all original infections, the likelihood of gametes ever even forming is practically a negative factor; while, on the other hand, original infections that receive improper treatment, or none at all, will develop them in a certain percentage of cases. There is also little doubt that a new infection responds to treatment much more readily than does one that has persisted for some time, and emphasizes the importance of an early diagnosis, for, as Celli writes, "the first step toward a good and rational prophylaxis is, as usual, the diagnosis of the disease, there being other morbid processes which simulate the malarial infections."

With the diagnosis early established, and followed by proper treatment being instituted and continued, the chief and most important prophylactic measure has been carried out.

In the preceding chapter we discussed the significance of the latent malaria carrier. A large proportion of these latent cases harbor the sexual forms of the parasite, which renders these individuals a menace to the community in which they reside, and it is the most serious problem that confronts any locality wishing to rid itself of malaria. It is imperative that, in all cases where there is reason to suspect malarial infection, an examination for plasmodia in the blood be made, and that in cases where they are found vigorous treatment be carried on until such time as repeated examinations of the blood show it to be sterile.

Much stress has been laid, by most writers in the past few years, on the necessity for mosquito extermination, but it should be remembered that there are two sources of infection: the mosquito, and man. Up to the present time work toward the eradication of the disease has been confined almost entirely to the destruction of the mosquito, little attention having been given to the other source of infection. It is true that a great deal of benefit has been secured by the use of screening material, but the use of this prophylactic unit has been more with the view of preventing mosquitoes giving the infection to man than man giving it to the mosquito. The presence of gametes, the macrogametes and microgametocytes, in the circulation of man is a most important etiological factor in the perpetuation of the disease, and their presence is the result of a process of evolution, and due in the large majority of,

if not in all, cases to improper treatment during and following acute clinical manifestations. In many localities mosquito extermination is impractical on account of the immense fund that would be required to rid a community, and to keep it rid, of the pest. In such localities, while I do not want in any way to detract from the valuable work that can be carried on by fighting the mosquito to the point of greatest possible reduction, it is very necessary that more attention be paid to the destruction of gametes in man; for, with this accomplished, myriads of mosquitoes may be present, but with their source of infection removed, they are rendered harmless, and unable to propagate the species of malarial organisms, when perforce malaria would disappear.

The administration of quinin in doses sufficient to prohibit the parasites developing in the circulation of man is an important prophylactic agent. Celli states, "He who takes quinin every day, and therefore has always a supply of quinin in the blood-stream, can undergo with impunity inoculations of blood full of malarial parasites, and can expose himself with little or no danger to the bites of infected mosquitoes." The results obtained in Italy following the prophylactic use of this drug are shown in the following table giving the number of deaths due to malaria from 1900 to 1907:

TABLE XVI.

Year.	Deaths.	Year.	Deaths.
1900	15,865	1904	8,463
1901	13,558	1905	7,845
1902	9,908	1906	4,871
1903	8,517	1907	4,160

There is a difference of opinion among authorities as to the requisite dose of the drug necessary for prophylactic purposes and as to the best time to administer it. Laveran advocates the administration of 0.5 gram every twelfth day, Koch 1 gram every eighth day, Ziemann 1 gram every fourth day, and Laborde 0.1 to 0.3 gram daily. A serious objection to the administration of the drug upon given days at fixed periods is that persons are likely to neglect taking the drug on the day that it is intended that they should, which results in it being taken at irregular intervals, and when results are not obtained the efficacy of quinin prophylaxis

is doubted. It has therefore been my custom to advise the taking of five grains of the sulphate of quinin every night upon retiring. By adopting this method, regularity is soon acquired, and the taking of the drug becomes a fixed habit for the period that is required to keep up the use of this prophylactic measure. By following this routine very excellent results were obtained by the author among a body of soldiers doing field duty in the Philippine Islands.

While quinin prophylaxis is a very valuable aid in the control and prevention of the disease, it should not be relied on to the exclusion of other prophylactic measures at our command, but when used in conjunction with other methods is of great value. It is especially valuable in cases of emergency, when one has to be exposed to the bites of *Anophelines* for short periods of time and is without adequate protection by screening or mosquito bars. Again, where a person is habitually protected by the latter methods, but owing to his occupation is suddenly taken away from such protection temporarily and exposed to infection, the use of quinin daily, in the dose mentioned, for a period of two weeks following such exposure, will often prevent an attack.

MEASURES DIRECTED AGAINST THE MOSQUITO.

Measures directed against the mosquito consist of their reduction by destruction of the adult insect or their larvæ, and may be considered under the following sub-headings: (a) physical, (b) chemical, and (c) biological means.

Physical Means.—The destruction of the adult mosquito in the home is a practical measure that is easy to put into force under any and all circumstances. Even the young children of the household can enter into this prophylactic work. Killing mosquitoes in the quarters has been given a great deal of attention in the Panama Canal Zone, Gorgas laying considerable stress on this prophylactic unit. Ross advocates the use of small hand nets, which render the capture of the adult insect an easy matter.

The removal of breeding places (Fig. 25), by drainage and filling in, is an important method of ridding a community of malaria. Where large areas of land have been drained to render them suitable for agricultural purposes (Fig. 26), such action has in many instances resulted in the complete disappearance of the disease where it was previously endemic. In localities situated near the coast line, and so situated that drainage is not feasible,

much can be accomplished by digging ditches, allowing the water to overflow these low areas at high tide. The author has reported the very successful results that were attained by this method, at Fort De Soto, Fla., an artillery post on Mullet Key, situated at the mouth of Tampa Bay. The mosquitoes at this post were very numerous, prevalent to such an extent that military routine and all outside work had to be suspended during certain of the warm months, but on an expenditure of six hundred dollars, which was

Fig. 25.—A typical breeding place for anopheles mosquitoes.

used in digging ditches to the edge of the bay, allowing the water to overflow the low areas at high tide, thus destroying the larvæ, the condition was improved 75 per cent.

It is not only in the large areas of swamp lands that the *Anophelines* breed, for their larvæ may be found anywhere where even the smallest collections of water are allowed to remain. It is common to find them where water has collected in cavities formed in decayed trees, in stopped-up gutters and eaves, washtubs, and other household utensils around the home, in which water is allowed to collect and remain undisturbed for some weeks, so that the motto of any community desirous of ridding itself of malaria should be

"no stagnant water." In lowlands where it is not feasible to drain, such areas may be filled in, serving the double purpose of destroying the breeding places of mosquitoes and reclaiming land valuable to the agriculturist.

The success that follows the destruction of mosquitoes and the removal of their breeding places was well shown at Ismalia, a town situated on the Suez Canal, with a population of 6,000. Malaria had been endemic there for over a hundred years, hundreds of

Fig. 26.—Large drainage scheme acting in double capacity of removing mosquito breeding places, and rendering land suitable for agricultural purposes.

cases occurring annually. In the beginning of 1902, active measures against the mosquito were instituted, with the following results:

Year	Number of Cases
1901	1990
1902	1548
1903	214
1904	90
1905	37

The place has since been practically free of the disease.

Equally as good results were obtained at Klang and Port Swet-

tenham, neighboring settlements in the Federated Malay States. Active measures to stamp out the disease were commenced in 1902 with the following results:

Years	1901	1902	1903	1904	1905
Cases	510	199	69	32	23

During these years the disease increased outside the zone in which operations were carried on.

Ross, in commenting on these operations which consisted mostly of drainage, states that most of the cases occurring in Ismalia, during the years 1904 and 1905, were cases of relapse among patients previously infected, and that the cost of this sanitary measure was about a thousand sovereigns ($5,000) per annum for three years, that at Klang and Port Swettenham the cost was about ten thousand sovereigns for permanent works, and about four hundred sovereigns for annual upkeep. He concludes by saying, "For them, as for Ismalia, the medical officers report that malaria has practically disappeared. The Health Officer proposing such campaigns must expect to be put to considerable trouble, but should remember that the work is part of his duties. The persistence of much malaria in any town can only be looked upon as proof of sanitary maladministration." The brilliant results obtained in these towns should not be anticipated in every town starting an active campaign against the mosquito, but there is no doubt that every dollar judiciously expended in mosquito eradication will prove to be money well spent in any community. It is very necessary that, with an initial expenditure for the destruction of mosquitoes, the work be carried on continuously, and means for so doing be provided, as it would oftentimes be a waste of money to initiate a campaign for the destruction of mosquitoes, and to cease operations at the end of a single season. The length of time that active measures have to be carried on will depend entirely on the topography and climatic conditions of the country.

Chemical Means.—A great deal of experimental work has been carried on in the past few years, in the hope of finding some practical means for destroying larvæ found in places that do not allow of drainage or filling in. One of the most satisfactory methods and one that has accomplished excellent results, in certain sections, is the use of kerosene oil, which rapidly spreads over the surface of the water, resulting in the death of the wigglers by mechanical

means—in coming to the surface for oxygen, they are unable to penetrate the oil film, their death resulting. The method should only be used in open bodies of water; ponds, in which weeds, grass, etc., are abundant, cannot be successfully treated, as such growth interferes with the oil spreading. The method is, however, especially valuable in treating small collections of water that cannot be drained. Howard was the first to introduce the method in 1903; Le Prince reports the use of a larvicide, consisting of carbolic acid, resin, and caustic soda, with which he has secured satisfactory results in Panama; he states that it is very effective, that a little of it goes a long way, and that a laborer can carry sufficient to carry on work for three or four hours.

Celli has conducted some extensive experimental work on the action of various larvicides; the following table gives the results of his observations:

TABLE XVII.

Action of Culicidal Substances on the Larvæ and Nymphæ of Mosquitoes (*C. pipiens, C. annulatus*). At the Ordinary Temperature (18 to 20° C.).

No.	Substances used.	Maximum time required to kill.	
		Larvæ.	Nymphæ.
		h. m.	h. m.
1	Saturated sulphurous water (SO_2)	10- 50	25
2	Potassium permanganate 0.3+HCl 5%	15	1
3	Salt water (saturated watery sol. NaCl)	30	1
4	Chrysanthemum powder (unexpanded flowers)	1 15	1 35
5	Chrysanthemum powder (second quality)	2 30	3
6	Petroleum c.c. 0.20 in 100 c.m.q. of surface	4	4
7	Potassium permanganate 2%	4	4
8	Ammonia 2%	5	6
9	Oil (very thin stratum, covering the whole surface of the water)	6	4
10	Petroleum c.c. 0.10 per 100 c.m.q. of surface	6	6
11	Potassium permanganate 1.5%	6	18
12	Chrysanthemum powder (unexpanded flowers) 0.006%	7	9
13	Formalin (formaldehyde 40%)	8	12
14	Carburet of lime 10%	8	8
15	Chrysanthemum powder (second quality) 0.06%	11	12
16	Lysol 0.1 to 0.5%	12	24
17	Milk of lime 10%	24	36
18	Commercial chloride of lime 1%	24	48
19	Commercial chloride of lime 1%	36	60
20	Potassium bichromate 1%	48	60
21	Potassium permanganate 1%	48	72

The same author's work on the effect of the aniline dyes is of great interest. The writer does not believe that this method has been applied in this country, and thinks it is one that should receive more attention. Its advantages over the petroleum method are best given in Celli's own words, who writes:

"The aniline dyes in general possess the useful quality of diffusing themselves in an extraordinary way in water, so that a very small amount colors a very large quantity of water. Moreover, very weak solutions are sufficient to destroy the young larvæ rapidly; and if the solution be made a little stronger, but still very weak, the adult larvæ are destroyed in twelve to twenty-four hours. Besides, while petroleum, being volatile, evaporates readily, the aniline dyes, on the contrary, remain active for a long time. In a large amount of water a solution of one of these two dyes remained active for more than two months, killing the larvæ in fourteen to twenty hours. The action is gradually lost when the water becomes putrid, which, however, in natural clear waters, where the larvæ of *Anopheles* develop, does not occur, or occurs to a much less extent.

Consequently these aniline dyes are of great practical value, especially as they are not poisonous to man or to mammals, so that the water that contains them in solution can be drunk by cattle.

They are, however, poisonous and deadly to many insects which live in marshy waters and cause damage to crops.

These waters, tinted with aniline colors, are not in the least injurious to plants, so that this system of disinfection can also be applied to the water of rice fields."

The three dyes with which he has conducted experiments are the green malachite, gallol, and larvicide.

The following table gives his results with these dyes:

TABLE XVIII.

Culicidal Action of Aniline Dyes on the Larvæ of Mosquitoes (Gen. *Culex*.).

Number.	Aniline dyes.	Proportion per mille.	Maximum time required to kill larvæ.
			h. h.
		0.50	6– 12
		0.025	24– 26
		0.0125	34– 48
1	Green malachite	0.0062	36–108
		0.0031	48– survive
		0.0015	survive
		0.0007	survive
		0.50	6– 12
		0.025	16– 24
		0.0125	24– 36
2	Gallol	0.0062	30– 72
		0.0031	36– 72
		0.0015	48–108
		0.0007	72– survive
		0.50	2
		0.025	2, 45
		0.0125	4
		0.0062	5
		0.0031	6
3	Larvicide	0.00125	7
		0.00062	9
		0.00031	16
		0.00015	24
		0.0007	48
		0.00031	72

The destruction of the adult mosquito by fumigation is an effective manner of ridding the home of the insect. While it is the natural tendency of the mosquito to leave the habitation of man at daylight, houses surrounded by dense foliage may harbor large numbers of the insect during the day as well as at night. The fumigation method is only practical in instances where a house, not adequately screened, is about to be, fumigation being used to kill those insects that are already within the dwelling. It is obviously absurd to fumigate a residence during the day to rid it of mosquitoes, only to have it filled up with others the same night, which would of course occur where screening is not in use. As mosquitoes will to a certain extent gain entrance in spite of screening, fumigation may be employed to kill such as succeed in getting in beyond the screens. Various fumigating agents have been used, among which may be mentioned, sulphur, tobacco, larvicide, pyrethrum powder, eucalyptus, iodoform, turpentine, camphor, formaldehyde, and ammonia. Boyce advises the use of sulphur, pyrethrum, or camphor and carbolic acid, and gives the following rules to be observed in using them:

Sulphur.—Allow 2 lbs. of sulphur to 1,000 cubic feet. Use two pots, place them in a pan containing 1 inch of water to prevent damage, and set fire to the sulphur by means of spirit.

Duration.—Three hours.

Pyrethrum.—Allow 3 lbs. to 1,000 cubic feet, and divide among two or three pots, using the same precautions as with sulphur.

Duration.—Three hours.

Camphor and Carbolic Acid.—Equal parts camphor and crystallized carbolic acid are fused together into a liquid by gentle heat. Vaporize 4 ozs. of mixture to each 1,000 cubic feet; this can be done by placing the liquid in a wide shallow pan over a spirit or petroleum lamp; white fumes are given off. To avoid the mixture burning, the fumes should not come in close contact with the flame of the lamp.

Duration.—Two hours.

Table XIX taken from Celli gives the results of his observations following the use of various odors, fumes, and gases, upon adult mosquitoes:

It is hardly necessary to state that before fumigation is commenced with any of these chemicals, all outdoor connections should be closed and stopped up in such a manner as to insure the fumes of the chemicals being held within the area intended to fumigate.

TABLE XIX.

Action of Culicidal Substances on Mosquitoes (*C. annulatus, C. pipiens, A. claviger*).

No.	Substances used.	Time in which death is manifested.	
		Apparent.	Actual.
	I.—Odors.	h. m.	h. m.
1	Odor of essential oil of turpentine	1	1
2	" " iodoform	10	40
3	" " menthol	10	45
4	" " nutmeg	10	2
5	" " musk	30	3
		4–	4–
6	" " camphor	5	5
		5–	
7	" " leek	10	5
8	" " crushed pepper	20	6
		10–	
9	" " naphthalin	35	8
10	" " Roman wormwood	6	24
		4–	
11	" " onion	6	survive
12	" " salvia		survive
13	" " rosemary		survive
14	" " dry and fresh basil		survive
15	" " cinnamon bark		survive
16	" " asafetida		survive
	II.—Fumes.		
			1–
1	Fumes of tobacco	instantly	3
2	" " larvicide	instantly	5
3	" " crysanthemum powder (unexpanded flowers)	5	1
4	" " valerian root	5	2
		3–	
5	" " fresh leaves of eucalyptus	5	3
6	" " quassi wood	16	5
7	" " pyrethrum powder	5	8
8	" " dry leaves of Mentha pulegium	5	8
		10–	
9	" " pitch	13	8
		2–	
10	" " dry leaves of basil	6	24
		7–	
11	" " dry rosemary	12	24
		2–	
12	" " culicidal cones	10	36
		2–	
13	" " dry camomile flowers	10	36
		2–	
14	" " dry leaves of Satureja hortensis	10	36
		8–	
15	" " salvia leaves	10	36
		5–	12–
16	" " wood	7	48
17	" " guaiacum resin	12	survive
18	" " myrrh	15	survive
19	" " elemi	15	survive
20	" " incense	15	survive
	III.—Gases.		
1	Sulphur dioxid	instantly	1
2	Hydrogen sulphid	instantly	1
3	Ammonia	1	2
4	Illuminating gas	1	2
			10–
5	Formaldehyde (Trillat's apparatus)	2	15
		15–	
6	Sulphuret of carbon	30	survive
7	Acetylene		survive

Biological Means.—The destruction of larvæ by small fish is a method by which mosquito reduction can be accomplished. A great deal of the success of this method depends on the locality and the fish introduced for the purpose; while many varieties of fish will eat the larvæ, there are certain ones that devour them more rapidly than others. Thus Ross speaks of the small goldfish which abound in the ornamental waters of Mauritius, which, he says, eat them but not voraciously; on the other hand minnows he saw in India would devour a dozen or more in a few seconds. He cites the description given by Boyce of the larvicidal propensities of the *Girardinus pœciloides,* popularly known as "millions." It is claimed by Gibbons that the immunity of the Barbadoes from malaria is due to the presence of these small fish which abound in the waters there. There has been but very little work done in the way of placing larvæ-eating minnows in the waters of America, where malaria is prevalent, and it is a matter that should receive more serious consideration in the future. It has the advantage of being economical, and the expense practically ceases with the original outlay, which is not true of most other methods of mosquito reduction.

There are certain other natural enemies of the mosquito larvæ. Galli-Valerio and De Jongh found that *Aspergillus niger* and *glaucus,* when introduced into water containing mosquito larvæ, killed them very rapidly. The larvæ of dragon flies are known to feed on those of mosquitoes, but their manner of feeding, which is on the bottom, makes them of little value in destroying such larvæ. Ross speaks of *M. Rossii,* a species of mosquito, which does not appear to be able to carry the malarial plasmodia, abounding in certain parts of India where malaria is not prevalent to the same extent that it is where this species of mosquito is not found. He considers it quite possible that plasmodia-bearing species are crowded out by this species, at least to the point below the malaria-bearing limit, although not exterminating them entirely. It is an interesting fact, which may be mentioned in passing, that De Vogel is of the opinion that the ability of the *M. Rossii* to convey malaria depends on whether or not it is bred in salt water. It is, we believe, the only species capable of breeding in both fresh and salt water, and attempts to incriminate it have been unsuccessful where fresh water was the breeding place, while De Vogel working with those breeding in salt water succeeded in infecting them.

MECHANICAL MEANS TO PREVENT THE MOSQUITO FROM GAINING ACCESS TO MAN.

Probably the most important action for individual families to take, upon moving into a malarial district, is the efficient screening of the dwelling. With the mosquito excluded from the home, the likelihood of infection is very materially reduced. In fact, where the occupation of the members of a family does not necessitate their leaving their own dwelling between sundown and sunrise, this measure will practically shut out all likelihood of infection. This

Fig. 27.—A modest dwelling with efficient protection against malarial infection.

was shown in the case of Doctor Sambon and his associates, who, while living in the Roman Campagna, took no other precautions against the disease than to retire to their mosquito-proof hut during those hours.

If protection is to be absolute, however, it is very necessary that extreme care be taken in the manner of screening, and it must be done in such a way as to positively exclude all mosquitoes. Not only must doors and windows be suitably screened, but also the verandas (Fig. 27). The author has frequently seen homes adequately screened, with the exception of the porches and verandas

used during the evening hours before retiring, this neglect resulting in many infections that probably would not have occurred if this additional precaution had been taken. The selection of screening material is of importance; the material used should depend entirely on the permanency of the protection. Thus, in temporary dwellings or in camp life, the ordinary cotton mosquito-netting may be used, and will prove very satisfactory, but in dwellings or permanent habitations, iron-wire netting, plain or galvanized, or better still, a copper-wire netting, should be used. While the last mentioned is considerably more expensive, it is probably the cheapest to use in the long run, as the life of a screen made with copper netting is of much longer duration than when made of other materials. The size of the mesh is of more importance than the quality of the screening used. Nothing larger than a number sixteen mesh should ever be used; this will exclude practically all mosquitoes, while an eighteen mesh is absolutely mosquito proof. The author has always advised that the wire screening be tacked upon the window casing, and the edges of the wire afterward covered with a narrow strip of molding. This does away with the expense of frames, and excludes the possibility of defective protection as a result of the frame later shrinking, creating an open space between the frame and the window. The common custom of using half screens, covering only the lower sash, is to be condemned, as it never gives permanent effective protection, except in cases where the upper sash is nailed in and a permanent fixture.

If immunity from malaria depends on protection from the mosquito, no matter how well the home is screened, the use of a mosquito canopy over the bed should not be dispensed with. There are so many opportunities for the insect to gain access, such as being carried in on clothing, etc., that in spite of all screening at least an occasional insect will gain entrance, in districts where mosquitoes are very numerous. Their use will be discussed more fully later. It is also advisable that all entrances to a dwelling be doubly protected against mosquito invasion, by a small vestibule having a screened door, in addition to the screened door on the entrance proper. Chimneys should be screened on the outside, or else the flues, not in use, should be closed by stuffing them with paper or other material.

The confinement of the infected individual, in quarters which are properly screened, is a provision that has been very much

neglected in even our most modern hospitals. With our present knowledge, that mosquitoes can only become infected from infected man, it is a matter of wonder that the isolation of the infected patient is not more generally observed, but as Craig writes, "Yet how seldom we see this precaution taken even in regions in which the malarial fevers are endemic and severe. We have seen that the mosquito is necessary as an intermediate host in the life history of the malarial plasmodia, and that the mosquito becomes infected by biting an individual suffering from malarial disease. From this it is obvious that, if we can place the infected individual in a position where the mosquitoes cannot gain access to him, the transmission of the infection will be impossible." Malaria should be made a reportable disease, and should be classified as a disease dangerous to the public health. There are at the present time many diseases in this classification that are attended with no greater danger to the public health than is malaria; and by making it compulsory to report and isolate it, much would be accomplished toward its prevention and control, and wherever such a law was put into effect it would do much toward the eradication of the disease. Patients suffering from malaria should therefore be placed in wards properly screened, and in private dwellings all such patients should be kept under mosquito canopies, at least during the hours between sunset and sunrise.

Wherever the mosquito prevails to such an extent that the discomforts attendant upon having mosquitoes biting during the sleeping hours are marked, the use of mosquito canopies has become very general. Too much carelessness is, however, the rule in the manner in which these canopies are used, for as a prophylactic measure they lose their value, unless proper attention is paid to detail. There is nothing more dangerous than a fancied protection against any disease, which as a matter of fact does not protect, and the manner in which the mosquito canopy is very often used is a striking illustration of this fact. The many points that have to be strictly observed, if all mosquitoes are to be excluded during the sleeping hours, may seem of minor importance, but only by their strict observance is full benefit derived. Ross has laid down the following rules that should be rigidly followed:

Not a single rent or hole in the net must be allowed. If there is one, mosquitoes, which spend the whole night in exploring every inch of the net in the hope of reaching the sleeper, are sure to find it and enter. Not only

should there be no rent or hole, but the net should be so hung that no aperture for entry is left. Thus it should always be hung inside the poles provided for the purpose, and tucked continuously all around the mattress. It should not be hung outside the poles, because then it cannot be tucked in satisfactorily in the manner mentioned; and it should not be allowed to hang down to the floor unless heavily weighted, because then it is apt to be blown up by the wind, thus allowing insects to enter. Moreover, if it is hung down to the floor, insects which are hiding under the bed during the daytime will often be included. The servant should be instructed to let down the net before dark in the evening, and to see that no mosquitoes are inside. If mosquitoes do find entry, it is always due merely to carelessness.

Do not have any opening for the purpose of entering the net. Such openings are often used in Europe and allow the insects to go to bed with the sleeper. When entering, one should lift the lower edge of the net from the mattress as little as possible and slip in with a twisting movement, so as to exclude stray mosquitoes, which may have been hovering around outside. If possible, use a large bed and a large net in order to avoid the hands, knees, and elbows being pushed against the gauze during sleep, and thus being bitten through the net by mosquitoes outside. If no large bed and net are available, this contingency should be guarded against by sewing a loose valance of gauze round the lower part of the net, about 9 inches (23 cm.) above the upper surface of the bed, the valance being tucked under the mattress together with the net.

While these directions are all important and should be observed in hospital practice, it is not to be expected that such perfection will be attained by the laity in any sections. It would be difficult to induce housewives generally to observe all of these details, but stress should be laid upon the importance of having nets constructed so that, when in use, it is impossible for a mosquito to find entry at any point. We think that a better method than tucking the canopy under the mattress is to have one large enough, and properly weighted, so that it will hang to the floor free of the bed, and some distance from it. Under this method it is impossible for the sleeper to unconsciously roll against the netting and be bitten, but if the netting hangs against the bed it is much better to tuck it in all around than to run the risk of movement of the bedclothes keeping it raised from the floor.

PUBLIC EDUCATION ON ALL MEASURES FOR THE CONTROL AND PREVENTION OF MALARIA.

The education of the public on all matters pertaining to the control and prevention of malaria is a most important step in a campaign for its eradication, for without public coöperation it is

impossible to secure results. Even in localities where the total eradication of the mosquito is feasible, such a measure generally calls for the expenditure of public funds, which expenditure will only be authorized when public opinion is in sympathy with the movement. More important still is it that the public should know the entire cycle of the plasmodia in both the mosquito and man; the full significance that improperly treated cases have upon the entire community; the fact that absence of clinical symptoms, following a few days of treatment, does not mean a cure of the disease; together with the details of the various prophylactic measures, and the necessity for a careful observance of all these entities.

During the past few years a great deal of work has been carried on in teaching the public that malaria is given to man by the mosquito, and much benefit has accrued from this educational campaign. It is now very necessary, and equally important, that the laity be also instructed on the fact that man gives malaria to the mosquito, that the way in which this is accomplished be explained, and that they be taught to fully realize the significant part played by man in the perpetuation of the disease. Such an educational campaign may be carried on through the columns of the daily press, and the articles written in such a manner as to be interesting and to attract public attention. A campaign has been recently carried on in the state of Florida, bulletins being published in all of the daily papers of that state, at intervals of a few weeks during the course of two summer seasons. The value of a continued and systematic educational campaign cannot be overestimated, as will be seen by the results obtained in Italy. The combined efforts of the Red Cross Society and the Society for the Study of Malaria in that country, in which educational work among the peasant classes has been a prominent factor, has resulted in a very marked reduction of the disease. Passed Assistant Surgeon McLaughlin in a report to the Surgeon-General of the United States Public Health and Marine Hospital Service, in commenting on the prophylactic measures taken in that country, writes, "To recapitulate, the war against malaria is conducted along these lines: the reclamation of marsh land, protection against mosquitoes, obligatory administration of quinin, and government control of quinin, insuring a pure drug at the lowest possible cost. These energetic measures are being carried out with persistence and assiduity. They are bound

to have, finally, the result hoped for—the extermination of malaria as an epidemic disease in Italy."

In considering prophylaxis in a general way, it should be remembered that measures that will bring about excellent results in one section will prove a complete failure in another. With our present knowledge it should be our aim to educate the public in such a manner that its hearty coöperation will be secured, as has been done in Italy, and what has been accomplished in that country is well pictured by Craig, who writes, "there is probably no one so ignorant in that country as to doubt the efficiency of the methods already instituted for the suppression of malaria, or who does not know why they were instituted, and how they are proving successful." With a properly instituted campaign in this country, there is no reason to doubt that equally satisfactory conditions could be brought about, and the author considers it the duty of every physician to work toward such an end; for the present status of malarial infections, and our failure to make any perceptible reduction in them, is not a credit to the medical profession, and reflects discredit on our nation in the sanitary world.

CHAPTER IX.

TREATMENT.

Quinin is so truly a specific in the treatment of the malarial fevers that a discussion of treatment of these infections is practically limited to: (1) the action of quinin on the parasites, (2) the choice of preparation, (3) the time for administering the drug and the amount to be administered, and (4) the method of administration.

HISTORY OF QUININ.

Mannaberg gives the following history of the introduction of quinin, being a translation by Binz from Markham's description:

> In 1638, the Countess of Chinchon, the wife of the Viceroy of Peru, lay very ill with tertian fever at Lima, the capital city. The news was carried to Canizares, then Corregidor of Loxa, a town among the Andes in the present Ecuador. Though the natives in Peru were unacquainted with the curative power of the bark, those of the more northern lying countries appreciated its worth, and from them Canizares obtained the secret. He, therefore, sent a parcel of it to the vice-queen. Her physician, de Vega, agreed to its employment, and she recovered in a short time. In 1640, the Countess returned to Spain and carried with her a large quantity of the precious bark, which she distributed about her native place in the vicinity of Madrid. De Vega followed and brought likewise a large amount of the bark to Spain, which he sold at Seville for a hundred reales a pound. The Countess employed the bark so extensively that for a long time it bore the name "Countess' powder" (pulvis comitissæ), and Markham asserts that even today the fame of her deeds in that region of Spain continues. The Jesuits, who were the missionaries to South America, also did good service in introducing the bark and spreading a knowledge of it.

As we have previously stated, the use of the drug was bitterly opposed by certain religious bodies, and it was not until the latter part of the seventeenth century that it was generally adopted for the relief of malarial disease. The adoption of the drug was soon followed by enormous amounts being administered, but that the custom was not universal is testified to by the fact that, while Ramazzini wrote that should a fever patient die it was considered

a crime not to have employed cinchona, he and others wrote vehemently against the abuse of the drug.

The alkaloid quinin was isolated from the cinchona bark in 1820 by Pelletier and Caventou, and the various salts of this alkaloid have since come into general use.

For many years, and until recently, it was maintained that the action of the quinin salts are only valuable on the asexual forms of plasmodia and that their action on the sexual forms is negative, but it is now known that all forms of the plasmodia in man can be eradicated by the proper administration of the drug. Darling was the first to demonstrate that by the continued use of a sufficient dosage of quinin a sufficient time, all sexual forms are destroyed, including those of the estivo-autumnal types, and in this demonstration has opened up a most important avenue in the prophylaxis of the disease.

ACTION OF QUININ.

That the administration of quinin in malarial infections cured the disease by a direct action on the plasmodia themselves, was first assumed by Binz in 1867, and in 1881, Laveran demonstrated that the parasites were killed by a 1 : 1000 solution of quinin, and stated that "it is because it destroys the parasite that quinin causes the disappearance of the manifestations of paludism." Since that time many investigators have studied the effects of the drug on the plasmodia, and much confusion has resulted, probably due to the staining methods used, many of which were imperfect, and to the interpretations arrived at from them. Craig, who in his own studies used the modified Wright's stain, which has been already described, has had exceptional opportunities in the Philippine Islands, Cuba, and this country for the study of the plasmodia, and has fully described the action of quinin on the different species of plasmodia as follows:

Plasmodium Vivax (Tertian Plasmodium).—The action of quinin upon the tertian plasmodium is evident in fresh blood specimens during every stage of the life cycle in man except immediately before sporulation. The changes produced by the drug consist chiefly in a granular degeneration of the protoplasm and fragmentation, the latter being most common in the nearly full-grown parasites. To these changes should be added a great diminution in the amount of pigment in the developing forms, thus showing a marked disturbance in the nutritive functions of the organisms.

The effect of the drug varies with the time of administration and the dose, but it is effective upon all but the segmenting bodies, and therefore is curative whenever given, whether in one large dose just before sporulation or in divided doses.

If quinin is administered when the young intracorpuscular plasmodia are present the changes produced by it are an increase in ameboid motion, followed in an hour by a decrease and finally by complete cessation; an increase in the refractive quality of the protoplasm; and finally granular degeneration of this portion of the plasmodium. During the stage of stimulation, the ameboid motion may become very active, the pseudopodia being projected so swiftly that it becomes almost impossible to follow the process. After the cessation of motion the young plasmodia become "ring-shaped" or spherical, and much more sharply outlined than is the normal tertian plasmodium. At this stage of growth no shrinkage of the organisms was observed as described by Golgi.

If now the blood be examined at regular intervals, the quinin being continued, it will be found that the plasmodia diminished greatly in number up to the time of sporulation, proving that at every stage of their growth quinin is capable of destroying them. Although this is so, a considerable number succeed in developing and finally reproduce by sporulation, but as will be shown in studying stained specimens, even these more fortunate organisms develop atypically, as the majority of the spores are sterile and incapable of further development.

In those plasmodia which perish prior to sporulation, quinin causes fragmentation, and eventually complete degeneration. Such fragmented parasites are very numerous in specimens of blood from tertian infections after the administration of quinin, and in those instances in which the drug has been given after pigment formation, fragmentation is the most common form of degeneration, but is always preceded by increased motility and by an increased refractive index. Numerous erythrocytes are observed containing plasmodia which are fragmented, the fragments containing pigment in most instances. The pigment may be motile or immotile, and is collected in the form of rather large blocks or masses. The protoplasm of the fragmented organism is always more refractive than that of the normal tertian plasmodium, and generally appears coarsely or finely granular. In many instances the fragmented parasites are extruded in whole or in part from the red blood-corpuscles and thus become free in the plasma, from which they quickly disappear, and in tertian infections after the administration of quinin it is very common to find many free degenerated plasmodia in the blood. Fragmentation of the tertian plasmodium due to quinin occurs at every stage in the human life cycle of the organism up to the sporulating form, but in the latter bodies I have never observed any evidence of this process.

While fragmentation of the plasmodia is very often the result of the action of quinin upon these parasites, it does not invariably occur, for many of the plasmodia present certain changes which do not eventuate in fragmentation. These changes consist in a marked shrinkage in the size of the organism, loss of the motility of the pigment, and increase in the refractive index together with granular degeneration of the protoplasm.

Upon the fully developed tertian plasmodium prior to the beginning of

sporulation, quinin exerts a marked action, causing a shrinkage of the organism, and a markedly granular appearance of the protoplasm, while the pigment becomes immotile, and is collected in large clumps throughout the protoplasm or is distributed about the periphery in small masses. Fragmentation may occur, but it is not as common as in the younger pigmented forms.

When quinin is administered just at the beginning of sporulation it produces no morphologic changes in the plasmodia, but if it has been present during the period of growth of the plasmodia it will be found that the sporulating bodies, which have evidently partially resisted the action of the drug, are smaller, appear more refractive than normal, while the number of spores is reduced.

There can be no doubt that quinin is very fatal to the young spores resulting from segmentation, while they are yet free in the blood-plasma, but it is not fatal to all of them, for in every case careful examination will demonstrate that some escape, penetrate the erythrocytes, and undergo more or less complete development. This can be demonstrated even in those cases of tertian malaria which do not present clinical symptoms of the infection, i.e., the latent cases.

From the changes which have been described it is evident that if quinin is administered when the blood contains the young intracellular plasmodia of tertian malaria it produces death in a certain number, while others are able to develop more or less perfectly, but are undoubtedly injured during every stage of their growth if the drug be given at regular intervals. This injury may result in death at a later period of development or by atypical development. If sporulation occurs, the spores are reduced in number, and as will be shown in the description of the stained specimens, most of them are sterile. Upon all forms of the pigmented tertian plasmodium until the beginning of sporulation quinin has a marked action, causing either fragmentation, shrinkage in size, or granular degeneration of the organism. The effect of the quinin upon all stages of growth of the plasmodium is most marked when it is administered in divided doses at regular intervals of time, thus keeping the blood supplied with it. If given just prior to the expected chill, in one large dose, the majority of the young plasmodia are destroyed while free in the blood-plasma, but those which escape and develop present but little evidence of the action of the drug, as would be expected, for the blood is free from quinin for several hours before the administration of the next dose.

In *stained* specimens of blood containing the tertian plasmodium the action of quinin is very clearly demonstrated. The modification of Wright's method already described was used invariably, and invariably the same morphological changes were observed after the administration of this drug. From my observations I have been able to confirm many of Romanowsky's published results, but I have been unable to demonstrate that the chromatin of any of the species of plasmodia loses its staining properties, but, rather, I have found that this important portion of the nucleus stains even more intensely than normal, but that the brilliant red color is replaced by a very dark violet or almost black. While this is true, it was invariably observed that the unstained portion of the nucleus had disappeared, and in those plasmodia which continued the developmental cycle, the chromatin had either failed to divide or

divided imperfectly, many of the spores showing no chromatin, as described by Mannaberg. The statement of Ziemann that the chromatin remains normal in appearance and divides as usual can only be true of those cases in which the quinin is administered just before sporulation, for if this drug be given during the formation of pigment the vast majority of the plasmodia which live to sporulate present either no evidence of division of the chromatin or division is imperfect, only a few of the spores showing any chromatin.

In order to study the morphologic changes occurring in the tertian plasmodia as the result of the administration of quinin it is necessary that the drug be given in divided doses to single tertian infections, the first dose just before sporulation; specimens of blood should then be taken at intervals of three hours and immediately stained. Given just before sporulation and repeated at intervals of every three hours, the quinin acts upon the plasmodia not only while free in the plasma, but also upon every stage of their life cycle in man, and it is thus possible to study the morphologic changes produced by quinin in every stage of the development of these organisms.

The young, unpigmented "ring forms" stain very intensely after the administration of quinin, the protoplasm a much darker blue than normal, while the chromatin stains a very dark crimson, often almost black. Besides the increase in the intensity of the stain, the loss of the unstained area about the chromatin (the vesicular portion of the nucleus) is very noticeable, and constitutes a most important evidence of the injurious action of the drug upon these parasites.

In tertian plasmodia a little further advanced in development, the staining reactions are the same as for the "ring forms," but the increased motility of the plasmodia is shown in the great number and "bizarre" arrangement of the pseudopodia. Fragmentation is observed even before the formation of pigment, some of the unpigmented plasmodia being broken up into deeply stained portions, the chromatin lying in one of these portions or free near the periphery of the red cell.

After the formation of pigment, and especially after the plasmodia are from one-half to three-quarters grown, the evidence of fragmentation and extrusion of the chromatin becomes more marked. Many of the erythrocytes contained deep blue portions of protoplasm, the chromatin lying free within the red corpuscle. The latter is frequently situated at the extreme periphery of the red cell, or even partly outside of it. At this stage numerous extracellular plasmodia are observed, either undergoing fragmentation or other forms of degeneration. Many of the fragments are entirely devoid of pigment, staining a deep uniform blue throughout, while some may be almost filled with blocks and granules of pigment. The vesicular portion of the nucleus is always absent, nor is there any evidence of an increase in the amount of chromatin which is so noticeable in the normal plasmodium when at this stage of development. If fragmentation be absent, the protoplasm of the plasmodium stains a very dark blue and the chromatin a dark violet or almost black. The pigment is generally collected about the periphery of the plasmodium. In many instances the chromatin is situated at the extreme periphery of the parasite or may lie partly or wholly outside of it within the erythrocyte,

proving that quinin possesses the power of causing extrusion of the chromatin, thus rendering the plasmodium sterile.

Together with absence of the vesicular portion of the nucleus there is seldom any evidence of increase in the amount of chromatin and of division of the latter.

In fully developed tertian plasmodia fragmentation frequently occurs, many of the fragmented parasites being free from chromatin, but the characteristic change at this period of development in those plasmodia in which fragmentation is absent, as shown by stained specimens, lies in the fact that, although the chromatin may be present and stains an intense violet, it has increased but little or not at all in amount, and division is either absent or imperfect, only two or three small masses being present, which lie close together near the periphery of the organism. In tertian plasmodia which have not been acted upon by quinin, and have reached this stage of development, the chromatin has always greatly increased in amount, and is found divided into numerous masses which are scattered throughout the protoplasm. The morphology of the plasmodia at this stage of their growth indicates clearly that quinin prevents an increase in amount of chromatin and either hinders division or prevents it altogether.

At this stage the protoplasm of the plasmodium stains a deep blue and the pigment is collected about the periphery in blocks or granules, or more rarely distributed throughout the protoplasm in the form of fine granules or small clumps. The vesicular portion of the nucleus is always absent.

Those plasmodia which sporulate after having been exposed to the action of quinin throughout their entire cycle of development present very marked morphological evidences of the injurious action of the drug, in stained preparations. While sporulation may not be entirely prevented, the majority of the spores are devoid of chromatin, and are undoubtedly sterile. The spores are also greatly decreased in number and may be distorted in shape, while in those which show the presence of chromatin the latter is in the form of minute irregular masses, very distinct from the compact spherical mass observed in normal parasites. Very often sporulating bodies are observed in which only two or three of the spores possess chromatin; in such spores the protoplasm stains a deep blue, the chromatin almost black, and there is no evidence of the vesicular portion of the nucleus. Associated with the chromatin containing spores are from six to eight, or perhaps more, deeply stained spores devoid of chromatin. In the sporulating plasmodia, the pigment, instead of being collected in a dense compact mass, as is the rule in the normal tertian plasmodium, is reduced in amount, and scattered in small clumps or granules between the spores.

From the changes demonstrated in stained specimens of tertian plasmodia after the administration of quinin it is evident that this drug, administered in divided doses, exercises a markedly injurious effect upon every stage in the human life cycle of this organism, either causing the death of the parasite at some period of its development or preventing normal sporulation by restraining the production and division of the chromatin prior to segmentation. The death of the organism is evidenced by fragmentation or extrusion of the chromatin, while the effect upon sporulation is shown by the lessened produc-

tion of this substance, the limited division of the chromatin present, and the number of spores which are devoid of this essential portion of the nucleus. The loss of the vesicular portion of the nucleus is probably responsible for the changes which are observed.

If quinin is administered in one large dose just prior to segmentation and the dose is not repeated, the changes produced are the same in kind as those described, but a very large number of the plasmodia escape entirely or are but little injured. When given in this way segmentation occurs as usual, and both the sporulating bodies and the individual spores appear normal.

Plasmodium Malariæ (the Quartan Plasmodium).—The changes produced by quinin in the quartan plasmodium, as shown by both fresh and stained preparations of blood, are practically the same as those described for the tertian plasmodium, and I cannot agree with Antolisei and Golgi that upon the adult quartan plasmodium quinin has no effect. In the young intracellular forms development is hindered or stopped, there being the same initial stimulation of ameboid movement, while in the older forms fragmentation and degeneration occur as frequently as in the tertian plasmodium. I have not been able to observe any difference, so far as morphologic evidence goes, in the effect of quinin upon the tertian and quartan plasmodia, although it is undoubtedly true that because of greater resistance to the drug, a larger number of quartan plasmodia escape destruction at the time of sporulation. As in the tertian infections, the effect of the drug is most apparent when it is administered in divided doses at regular intervals.

Plasmodium Falciparum. Plasmodium Falciparum Quotidianum (the Tertian and Quotidian Estivo-Autumnal Plasmodia).—As the effect of quinin is the same upon both species of estivo-autumnal plasmodia, I shall consider them together. As stated in the historical summary, Marchiafava and Bignami found that in fresh specimens, after the administration of quinin, the plasmodia assumed a discoid form and left the erythrocytes, while the motility was normal or increased. While I have been able to confirm the occurrence of the discoid shape, I have not been able to confirm their observations regarding the exit of the plasmodia from the red cells. The following observations are based upon the study of the action of quinin upon both fresh and stained specimens of blood containing the estivo-autumnal plasmodia, including every form of the organisms except the fully developed pigmented bodies and the sporulating bodies.

In fresh specimens, a few hours after the administration of quinin in divided doses, the time varying with the rate of absorption of the drug, the hyaline "ring forms" become much more refractive and sharply cut than normal, while the ameboid motion is always greatly stimulated. In most instances, the "ring forms," owing to the great increase in the activity of the ameboid motion, lose their distinctive form, becoming discoid or assuming irregular shapes, and not infrequently change their position in the red corpuscle very rapidly, occupying the same portion of the cell only a few seconds at a time, but I have never observed their exit from the red corpuscle.

Upon the larger pigmented forms, and pigmented "rings," quinin appears to have less effect, the only change observed in fresh specimens being an increase in the refractive index, while the outline of the plasmodia becomes more

sharply defined. I have not observed degeneration by fragmentation in the estivo-autumnal plasmodia, although it is so common in the tertian and quartan parasites.

In *stained* specimens the results of my observations are opposed to those of Marchafava and Bignami, who claim that no morphologic changes occur in these plasmodia after the administration of quinin, and that the unpigmented parasites do not become pigmented after its administration. I have repeatedly observed pigmented forms of both the tertian and quotidian estivo-autumnal plasmodia develop after quinin had been administered for as long as three days, while the morphologic changes produced, though not so marked, are similar to those observed in the tertian and quartan plasmodia.

In the "ring forms," which are most easily studied, the staining capacity of both the protoplasm and the chromatin is increased, but the unstained area surrounding the chromatin disappears. A large number of the "ring forms" may appear normal, but careful examination will demonstrate that most of them show the loss of the vesicular portion of the nucleus and that the "rings" are distorted in shape owing to the increased ameboid motion. In a few instances I have observed the separation of the chromatin from the body of the plasmodia, thus proving that extrusion had occurred. I have never observed fragmentation of the "ring forms."

The changes produced in the young pigmented forms of the estivo-autumnal plasmodia, as shown in stained preparations, are similar in every respect to those occurring in the tertian and quartan plasmodia, consisting in fragmentation, loss of the vesicular portion of the nucleus and extrusion of the chromatin. . . .

Upon *intracorpuscular conjugation* quinin has a fatal influence, for, after the administration of this drug, conjugating plasmodia entirely disappear from the peripheral blood and do not reappear unless the administration has been stopped, and then only after an interval of days or even weeks. Even in those instances in which the drug is given in such small doses as to injure but slightly the developing plasmodia, the conjugating organisms quickly disappear, and as the process of conjugation is undoubtedly intended to assist in maintaining malarial infection, the marked action of quinin upon it offers another explanation of the efficiency of the drug in curing these fevers if it be properly given during the initial attack.

In 1908–1909, Darling carried on a series of experiments in Panama for the purpose of determining the limit of infectiousness of man, and the effect of quinin on the number of gametes in the peripheral blood. He writes:

To me this appeared to be, if possible, worth determining, because in the discharge of patients from the hospital it would be manifestly unwise to turn a patient out, although free from symptoms, yet with gametes enough in his peripheral blood to infect every susceptible anopheles mosquito that might bite him.

His observations established the fact that gametes are eradicated from the circulation if quinin is persisted in. He states:

The effect of quinin administration on the number of gametes in the peripheral blood was studied in a number of patients suffering from estivo-autumnal and tertian fever by the administration of 30 grains quinin daily, either with or without iron and arsenic, and by withholding quinin and merely requiring rest from labor. In estivo-autumnal infections, when there were crescents in the blood, the number was reduced by quinin, 30 grains daily, at the following rates. For example, in Experiment 17 there were:

9 crescents per 100 leucocytes on December 26
5 crescents per 100 leucocytes on December 27
5 crescents per 100 leucocytes on December 28
4 crescents per 100 leucocytes on December 30
1 crescent per 100 leucocytes on December 31
0 crescents per 100 leucocytes on January 2
0 crescents per 100 leucocytes on January 13

Other cases showed the following evidence of the action of quinin treatment: a case showing 67 gametes per 100 leucocytes was reduced to 1 per 200 leucocytes in 25 days; another from 92 gametes per 100 leucocytes to 1 per 100 leucocytes in 15 days; and one with 9 gametes per 100 leucocytes was negative in 8 days, while in another case in which quinin was withheld, crescents remained constantly for 23 days, there being 16 crescents per 100 leucocytes on admission, and 20 per 100 leucocytes at the end of the period. He concludes that:

Patients having crescents or tertian gametes in their peripheral blood should not be discharged from the hospital, nor should treatment be discontinued until gametes have been reduced to a non-infectious minimum. The destruction and prevention of development of the sexual parasites in man is of great importance and may be accomplished: (1) by appropriate quinin treatment of all gamete-carriers entering the hospital; (2) by occasional quinin treatment to destroy latent malaria; (3) by the periodical examination of laborers in quarters where there is a high malarial rate for the detection of gamete-carriers and latent malaria in order to carry out appropriate treatment.

Thirty grains of quinin sulphate in solution daily is an efficient dose for the purpose required.

Bass is of the opinion, in which most authorities concur, that the destruction of gametes is not the result of the direct action of the drug upon them, but that their eradication is secured by destroying the schizonts, their source of origin, and that, with these removed, the sexual forms in the circulation finally die of old age.

The effect of quinin on the formation of gametes has been studied by Thomson, who reports his observations of a case in which 850 crescents per cubic millimeter of blood followed a first paroxysm

accompanied by 50,000 asexual spores per cubic millimeter. Twenty grains of quinin were given during this paroxysm, but no more was given for several days before or after it. The next paroxysm where no quinin was given until the day after produced 468 crescents per cubic millimeter, and the next only 344 from 54,000 of the asexual forms per cubic millimeter. At this period thirty grains of quinin were given daily, and a later relapse gave only four crescents per cubic millimeter, from asexual spores numbering 16,000 per cubic millimeter.

CHOICE OF PREPARATION OF QUININ.

While there are several salts of quinin which may be used in the treatment of malarial infections, the author has found it necessary to employ but a few of them. In the vast majority of cases the drug can be administered by mouth, and for this purpose, on account of its being cheaper, and in more general use, the sulphate will be found to give entire satisfaction. In young children, or in those who have difficulty in swallowing capsules, euquinin will be found a very useful preparation; it is very much superior to the tannate, a salt that has been popular in treating young children. For hypodermatic use the bimuriate of quinin is the one of choice. The following table from Manson, with certain modifications by Rosenau and Anderson, shows the solubility and equivalent value of the various salts of quinin:

TABLE XX.

Solubility and Equivalent Value of Salts of Quinin.

Name of salt.	Percentage of the alkaloid in the salt.	Solubility in cold water.	Amount sulphate. of quinin value to one equivalent in
Sulphate	73.5	800 parts	1.00
Hydrochlorid	81.8	40 "	.9
Bihydrochlorid (*a*)	72.0	1 "	1.02
Hydrobromid	76.6	45 "	.96
Bihydrobromid	60.0	7 "	1.23
Bisulphate	59.1	11 "	1.24
Phosphate	76.2	420 "	.96
Valerianate	73.0	110 "	1.01
Lactate (*a*)	78.2	10 "	.94
Salicylate	70.1	225 "	1.05
Hydrochloro-sulphate (*a*)	74.3	2 "	.99
Arseniate	69.4	slightly soluble	1.06
Euquinin	81.8	slightly soluble	.89
Tannate	20.0	slightly soluble	3.67
Bichlorid of quinin and urea	59.2	1 part	1.24

TIME AND AMOUNT OF ADMINISTRATION OF QUININ.

There has been a great deal of discussion as to the best time to administer quinin in malarial infections. We have seen that the drug has a direct action upon all malarial plasmodia except the presegmenting forms, so that it is hardly necessary to discuss at length the various theories as to the proper time for the administration of the drug. The three principal methods that have been under more or less discussion by modern writers are: (a) Torti's method, consisting of a single dose of about fifteen grains a few hours before the expected paroxysm, proceeding on the theory that the parasites are more easily destroyed by the drug immediately following sporulation. A great objection to the single dose lies in the fact that in cases presenting other than a typical picture the time of sporulation cannot be anticipated with any degree of accuracy. (b) Sydenham's method consists of a similar dose given during the decline of the paroxysm, and while it is not open to the same objection or to an equal degree, it is not always easy in certain cases presenting irregular symptoms, especially in mixed or double infections, to tell just when the stage of decline is upon the patient. Another objection to both of these methods is the fact that the large single dose is oftentimes not well tolerated by the patient: and (c) Manson's method, which consists of the administration of ten grains at the commencement of sweating, followed by five grains every six or eight hours for the next week, and after that five grains three times on one day of the week, or fifteen grains in a single dose once a week, for six weeks or two months longer.

The author has adopted a slight modification of this method, giving five grains of the sulphate every four hours during clinical manifestations; after the subsidence of symptoms five grains three or four times daily for ten days or two weeks; and after that ten grains, in two or three doses, every alternate day for at least a month. In those cases seen early in the infection this method will generally control the clinical manifestations within forty-eight hours. In old recurring infections, however, and especially in the estivo-autumnal types showing both asexual and sexual forms, it is necessary to use larger doses and for a longer period. In such infections, ten grains three times daily should be administered for at least three weeks, after which period the dose may be reduced to twenty grains per day for an additional two weeks.

An interesting point has recently suggested itself to the writer. He has noticed that in all original cases that have come under his observation early in the disease, and in which he was able to carry on efficient treatment a proper length of time, not a single reinfection was seen, while reinfections or recurrences, or both, are common among those who will not submit to a proper and continued treatment. It suggests the important possibility—does early and efficient treatment in original infections produce a relative immunity to later reinfection? It may be possible that the rapid destruction of the young parasites results in the formation of antibodies that confer an immunity for a certain length of time.

While the time of administration in benign tertian or quartan infections may not be of great importance, Craig is of the opinion that "in estivo-autumnal infections quinin should never be administered in one large dose during the twenty-four hours, as such treatment invariably results in the febrile condition persisting for several days, during which time pernicious symptoms may develop." He states that he has observed "serious results follow the administration of quinin in this manner, some of the patients so treated dying from pernicious attacks which might have been controlled had the drug been administered in divided doses at regular intervals." His results in the treatment of estivo-autumnal infections with quinin administered in divided doses, in many hundreds of cases, have been uniformly satisfactory, and the author has found that in nearly every instance the clinical symptoms subside, under this method of treatment, within three days, usually within forty-eight hours. The author considers, therefore, that the most satisfactory method of giving quinin in all malarial infections is in divided doses at regular intervals. The enormous doses of the drug that have been advocated by some, in even recent years, have never been found necessary, and it can safely be stated, without fear of successful contradiction, that a fever that will not respond to thirty grains given within twenty-four hours in divided doses is not of malarial origin, or at least is accompanied by some complicating process. In making such a statement we anticipate that the drug is given in such form as to insure its being absorbed.

METHODS OF ADMINISTRATION OF QUININ.

Quinin may be given (a) by the mouth, (b) hypodermatically, (c) intravenously, or (d) by the rectum.

By the Mouth.—In a great majority of cases quinin administered by the mouth gives satisfactory results. It may be administered in this way in all cases except those developing pernicious symptoms, when it becomes necessary to secure more prompt action of the drug, or in those cases in which vomiting is a prominent symptom during the first few hours of an attack. It is advisable that the drug be administered in some form that will eliminate the bitter taste, objectionable to most people, and for this purpose the author has always found a gelatin capsule the most satisfactory. The use of pills and tablets is to be condemned, as they are often more or less insoluble, and never liberate the entire dose as rapidly as a gelatin capsule. By using a high-grade capsule and prescribing with it ten or fifteen drops of dilute hydrochloric acid, well diluted, one can be assured that the contained quinin will be freed in the stomach and properly absorbed. There are some that advocate the administration of the drug in solution, but it is such an unpleasant dose to the majority of patients that the author has seldom so used it for adults. For children, however, it is his practice to use solutions entirely, and he has found the syrup of yerba santa, or the syrup of orange peel, a satisfactory vehicle. In treating adults it is his custom to employ the sulphate almost exclusively, while the ethyl-sulpho-carbonate, put on the market under the proprietary name of Euquinin, is a most satisfactory salt for employment among younger patients, and being tasteless, may be given either free in powder form, or combined with any of the aromatic syrups. For prophylactic purposes among children the tannate, in the form of chocolate lozenges, may be used to advantage.

Hypodermatically.—Hypodermatic administration of the drug is the method of choice in all cases of pernicious malaria, in which it is desired to get prompt action of the drug. It will also be found of great value when the stomach is very much upset during the onset of a paroxysm and rejects anything that is swallowed. The author has seen many severe benign tertian infections where vomiting was so persistent that administration by the mouth was out of the question, which quieted down with a single hypodermatic injection, so that medication by the mouth could be continued during the rest of the illness.

By observing proper precautions the fear of abscess formation need not deter one from using quinin hypodermatically; the quite common opinion that abscess is a necessary sequela to its hypoder-

matic use being an error. A glass syringe with solid-glass piston should be employed, and with the needle, should be boiled for at least ten minutes. It is the author's practice to wash the site of injection with soap and water, dry, and paint it with tincture of iodin. Instead of placing the solution subcutaneously, the needle should be driven well into the muscular tissue; this method first advocated by Koch is less painful and fully as efficient as the subcutaneous method. The author has employed, for hypodermatic administration, for some years with generally satisfactory results, ampuls containing 0.30 gram of quinin bihydrochlorid carbamid, which can be secured from the Kny-Scherer Co., of New York. The dose employed in pernicious cases has been from one to three ampuls in adults, while in children the dose is graded according to their age. These ampuls will be found a great convenience to the country practitioner who may at any time be called upon to administer a sterile solution under circumstances that do not favor the home preparation of such solutions, and in malarial zones we consider no physician's armamentarium complete without a package of these ampuls.

Many solutions have been recommended by various authorities for injection purposes, among them may be mentioned the following, Kobner recommends:

Quininæ hydrochloridi	.5–1 gm. (gr. viij–xv)
Glycerini	
Aquæ distillatæ āā	2 gm. (ʒ ss)

Triulzi:

Quininæ hydrochloridi	3 gm. (gr. xlv)
Antipyrinæ	2 gm. (gr. xxx)
Aquæ	6 gm. (ʒ iss)

Deaderick:

Quininæ bihydrochloridi	1 gm. (gr. xv)
Aquæ	10 gm. (ʒ iiss)

Intravenously.—Baccelli was the first to use the intravenous method, in 1890; he advocated its employment where it was necessary to get prompt effect, using the following formula:

Quininæ bihydrochloridi	1 gm. (gr. xv)
Sodii chloridi	0.075 gm. (gr. iss)
Aquæ distillatæ	10 gm. (ʒ iiss)

The usual precaution in the preparation of the site of injection should be carefully observed; the syringe and needle and solution should all be sterilized; and the solution when injected should be about body temperature. A tourniquet applied above the elbow will render the veins prominent; one well distended is then chosen, the needle introduced from below upward, and the entire quantity of the solution slowly introduced. The needle is then withdrawn, and the site of puncture sealed with iodoform collodion. Baccelli claims to have had a greater degree of success with the administration of quinin in this manner in pernicious cases than with the subcutaneous method, and states that where the mortality in pernicious cases treated by the subcutaneous method was 17 per cent, he has reduced it to 6 per cent by using the drug intravenously.

By the Rectum.—While the administration of quinin by the rectum has been advocated by many authorities in the past, the method is not one that the author would recommend, except possibly in the treatment of young children. Absorption takes place very slowly, making larger doses of the drug necessary, and such administration cannot be continued on account of the local irritation that follows its use, so that except in exceptional instances it is not of much value. Where it is employed, at least double the amount of the drug that would be given by the mouth should be used, the solution should be a weak one, with ten drops of tincture of opium added to it, and the injection made high up.

While there are a great many people who will claim that they are unable to take quinin, it is seldom that a true idiosyncrasy exists, or, if present at all, that it is of sufficient degree to justify the discontinuance of the drug. An idiosyncrasy may however exist, and in exceptional cases is present to such a degree that even the smallest dose of the drug is absolutely prohibited. No attention should be paid to the tinnitus aurium, vertigo, or other unpleasant symptoms that generally occur in all individuals when the drug is used in the necessary dosage; but when syncope, extreme dyspnea, amaurosis, or total deafness occur, it is advisable that the drug be withdrawn or at least very cautiously used.

OTHER METHODS OF TREATMENT.

While quinin is a true specific in the treatment of all malarial infections, it is well to bear in mind other lines of treatment, on account of the occasional patients with whom we come in contact

that really are unable to take it. None of them will compare favorably with the specific, but may nevertheless give fairly satisfactory results.

Methylene Blue.—This drug was first advocated by Guttman and Ehrlich, in 1891, and its use has been advocated by many others since that time. It is, like all substitute treatments, more or less unsatisfactory, and the reports from different investigators are somewhat at variance. Only the medicinal methylene blue should be employed, and it is best administered in three-grain doses four or five times during the twenty-four hours. An objection to its use is the strangury so commonly followed by its administration; this can be relieved by using a few grains of powdered nutmeg in conjunction.

Thayer reports having seen a case relapse while in bed under continued treatment with methylene blue, and while he has seen it used with a certain degree of success, writes, "My own experience confirms that of most observers that its efficacy is far below that of quinin, and uncertain."

Craig states, "I have used this drug but seldom and have found it unreliable. In rare instances it will effect a cure, but it is not to be compared to the salts of quinin in efficiency."

Thomson, who has studied its effect on the crescents, concludes as follows: "It would appear from the careful investigation of six cases treated with methylene blue alone, that this drug in doses of twelve grains daily, given by mouth (pill form), though not so potent in destroying the asexual parasites, is yet more potent than quinin in preventing crescent formation. It would seem also to have some direct destructive effect on the crescents. It is good treatment, therefore, to give methylene blue along with quinin, especially where one cannot give large doses of the latter due to the idiosyncrasy of the patient."

Deaderick considers that, "it is the best substitute for the derivatives of Peruvian bark. While it does not compare favorably with quinin, requiring a longer time to effect a cure, and failing altogether in not a few instances, it seems to possess some specific action upon the parasites of malaria, and is the most valuable drug where the cinchona preparations are absolutely contraindicated."

Picric Acid.—This has been recommended in malaria by many writers. Surveyor, who has recently carried on some investigations with it, was unable to get any results in a case of benign tertian,

but reports successful results in the treatment of cases with crescents. His studies comprised 18 cases which had picric acid by mouth, 4 cases which had injections of picrate of soda (3 cubic centimeters daily of a 4 per cent solution), and as control to the picric acid treatment 28 cases which had quinin (with injections in six cases), and 6 cases which had quinin together with mercury, arsenic, etc. The dose of the picric acid given was 2 grams two or three times daily. His method of preparing the solution of picrate of soda for injection is as follows:

Add 4 grams of acid picric to about 75 cubic centimeters of boiling distilled water, and to this add, drop by drop, a strong solution of sodium hydrate, taking the reaction at the same time, with a solution of di-methyl-amido-azo-benzol, until the latter no longer turns red. (Do not stop when the dimethyl turns red and subsequently fades, but go on adding the sodium hydrate solution till no change of color occurs.) Confirm with phenolphthalein to see that no change of color occurs; this latter is necessary to ascertain whether the solution has become alkaline or not. At this stage, most of the picric acid is dissolved. Make up the solution to 100 cubic centimeters with distilled water; 3 cubic centimeters of this solution is put up in test-tubes and sterilized at 120° C. in the autoclave. As the water evaporates in these tubes crystals are deposited, which can be readily dissolved either by slightly warming the tube or adding a few drops of sterile distilled water. The injections are no more painful than ordinary injections of vaccine, and do not produce any marked reaction, nor is there any nodule or swelling noticed at the site of injection. Scarcely any pain is present at the end of twenty-four hours, so that there is no difficulty in injecting about 3 cubic centimeters of this solution on consecutive days.

The following table showing his results is of interest:

TABLE XXI.

Nature of cases.		Cured.	Died.
(No. picric.) Malignant tertian with rings and crescents	34	25 (73.53%)	9 (26.47%)
(Picric treatment.) Malignant tertian with rings and crescents	22	19 (86.37%)	3 (13.63%)

He states that the injections of picrate of soda were not found to produce any quicker results than the method of administration

of picric acid by mouth; and that it was only employed where the patients would not take medicine readily.

His results, to say the least, justify further experimental work, especially in cases that do not stand well the long-continued administration of quinin that is necessary to eradicate the sexual forms of the estivo-autumnal infections.

Treatment with Roentgen Rays.—Schaudinn was the first to study the effects of Roentgen rays upon certain protozoa, but his efforts were not productive of satisfactory results. More recently Skinner and Carson have carried on some work and seem to have secured more satisfactory results. They applied the rays in six cases, giving an exposure of five minutes, which was followed in every instance by a subsidence of clinical symptoms. They do not state the type of malaria that was present in these cases, or as to whether there was a disappearance of the plasmodia, but state, "Our experience has been that the application of x-rays in cases of malarial fever relieves splenic pain and reduces recent engorgement; that the temperature falls and does not usually rise again; and that recovery is not attended by the anemia usually present in cases treated with quinin. We have not had to fall back upon quinin in cases treated by the x-rays, while we have had cases which resisted quinin and yielded promptly to the rays (quinin being discontinued)." While it may later be proved that this line of treatment will secure results, the scope of its usefulness will unfortunately be limited, as the necessary paraphernalia will not be obtainable where the greatest number of cases occur.

Other Drugs.—Various other drugs have been mentioned as substitutes for quinin, but none of them are worthy of mention. Recently salvarsan has been heralded as a panacea for many infections, including malaria, but the author sees no excuse for the administration of a drug which admittedly has an element of danger in its administration, when we have as comparatively as harmless a specific for the infection as quinin. Sodium cacodylate in like manner has its enthusiastic supporters in the treatment of any condition suggesting the administration of arsenic, but there is no evidence up to the present time that this drug is of any special benefit in the treatment of malaria.

Efforts have been made to secure a serum treatment for malaria, Kuhn, Hovorka, and Ford have carried on investigations with this end in view, but their results have not been satisfactory.

GENERAL MANAGEMENT OF ACUTE MALARIA, AND TREATMENT OF SPECIAL SYMPTOMS.

All patients suffering with acute malaria should be placed in bed at least for the period covering acute clinical manifestations, and it is advisable that effort be made to keep them in bed for a few days after the subsidence of these symptoms, especially in the estivo-autumnal infections. A purgative should be administered, it being the author's practice to give five grains of calomel, followed in a few hours with a saline. The general management of the case should have in view the comfort of the patient, in so far as is consistent with proper treatment. During the cold stage, heat should be employed externally by the use of hot-water bags; while this will have no effect on this stage of the paroxysm, it is gratifying to the patient. During the period of fever, cool drinks such as lemonade may be given, and if the pyrexia is excessive it should be combated by baths of tepid or cold water, or sponging with water and alcohol. Nothing is to be gained by the administration of antipyretics. The old theory, still more or less popular among the laity, that quinin should not be given during the height of the fever has been discarded, and it is well that quinin be administered as early as the diagnosis is established. The disagreeable effects following single large doses, which tend to increase the headache and general discomfort of the patient, will not be experienced if the drug is given in divided doses, as has been already recommended; in fact, the headache will disappear sooner if treatment is promptly commenced than it will in untreated cases. The patient should be placed on a liquid diet, consisting of the gruels, milk, or broths. This diet may be elaborated on as soon as it is evident that the attack is under control, and the patient gradually returned to a full and nutritious diet. Any special symptoms that develop during or following an attack should be met symptomatically. In cases of cardiac weakness aromatic spirits of ammonia, strychnin, and brandy may be used. If the headache or general pains are especially severe they may be controlled by opium; but the author does not favor such treatment except under exceptional circumstances, and where it is necessary to use it, codein is the preparation of choice. In addition to the treatment by quinin, iron in some form, arsenic, and strychnin will hasten convalescence. It is the author's practice to use the following formula:

Quininæ sulphatis ..... ʒ iss
Ferri reducti ..... ʒ ss
Strychninæ sulphatis ..... gr. i
Arseni trioxidi ..... gr. ss
Misce et fiant capsulæ No. xxx.

The patient is instructed to take one of these capsules three or four times a day, and in addition takes what other quinin is necessary for the complete eradication of the infection, as previously discussed in considering the administration of quinin.

TREATMENT OF MALARIA IN THE PREGNANT WOMAN.

It may be generally stated that all cases of malaria in pregnant women should be treated regardless of this condition. By this, it is not meant that care should not be observed in the administration of the specific, or that its use is not liable to bring on the expulsion of the fetus. The disease if allowed to persist will itself produce uterine contractions, and the author is satisfied that pregnant women treated for malaria will not abort as frequently as those not treated. If possible, a laboratory diagnosis of malaria should be secured, and the blood carefully watched during the period of treatment and at certain regular intervals following the withdrawal of treatment. Quinin should be given only in sufficient doses to control the symptoms, the dose, therefore, depending entirely on the intensity of the infection and the degree of resistance of the patient. The author has found the following formula of value:

Quininæ sulphatis ..... ʒ iiss
Extracti hyoscyami ..... gr. viiss
Misce et fiant capsulæ No. xxx.

One of these capsules is given every six hours, and the patient kept absolutely at rest in bed for several days after the subsidence of all symptoms. If uterine contractions become evident, and the clinical symptoms of the infection are not severe, the treatment is temporarily suspended, to be later renewed. No attempt should be made to entirely eradicate the infection during the pregnant state, regardless of the manner in which the patient behaves under the treatment, but to simply keep the infection under control until after delivery, when treatment can be consistently carried on.

TREATMENT OF PERNICIOUS FEVERS.

The treatment of malarial infections developing pernicious symptoms differs, from that in other types, only in the necessity for prompt absorption of the specific. On this account the drug should always be administered hypodermatically, either intramuscularly or intravenously, in the manner already described. The various symptoms that may develop in the various types are treated symptomatically. The intense hyperpyrexia should be treated hydrotherapeutically, or by the application of the ice bag; cardiac weakness with stimulants; in choleriform cases the bowels should be controlled with opium by mouth, and normal saline solution administered by hypodermoclysis; and in the bilious remittent types the vomiting should be controlled by counter-irritation applied over the epigastrium, or the administration of an emetic which will often allay this symptom. All cases developing pernicious symptoms should have thorough intestinal elimination. The administration of the specific will usually control convulsive movements, but in cases that do not respond to it, opium or chloral may be administered. Inhalations of chloroform will often be found of great service in convulsions, especially in the treatment of children.

TREATMENT OF CHRONIC MALARIAL CACHEXIA.

Following repeated infections a chronic cachetic state, which is very obstinate in responding to treatment, may result. The plasmodia will often be hard to detect, and the only apparent condition is one of general anemia usually associated with an enlarged spleen. Treatment calls for persistence; quinin combined with arsenic, iron, and strychnin should be employed for prolonged periods. It is in this form that arsenic, in the form of Fowler's solution, can be used to great advantage; the dose should commence with a drop or two drops three times a day and be gradually increased to the full physiological limit. The solution of iron and acetate of ammonia (Basham's mixture) will also be found of service. Craig recommends the following formula, known as the esanophele pill:

Quininæ bihydrochloridi	0.1 gm (gr. $1\frac{1}{2}$)
Arseni trioxidi	0. 001 gm (gr. $\frac{1}{64}$)
Ferri citratis	0.15 gm. (gr. $2\frac{1}{4}$)

Each pill to contain the above.

Dosage: Children, 3 to 6 years,
1 pill at 6 A. M. and 1 pill at 6 P. M.
7 to 14 years,
2 pills at 6 A. M. and 1 pill at 6 P. M.
Adults,
2 pills at 5 A. M., 2 at 8 A. M., and 1 at 6 P. M.

A change of climate will often do more for these patients than many weeks or months of treatment, and on this account, whenever their financial condition will permit of such a change, it is advisable to have them go to the mountains or seashore.

Except where the plasmodia are active, nothing will be gained in these cases by the use of large doses of quinin. It should be the aim of the attending physician, however, to keep the blood constantly charged with the drug, giving it continuously, and combining with it those drugs that are known to have a reconstructive action on the blood constituents. The patient should be warmly clad, and well nourished, avoid all excesses, and in so far as the conditions will allow, lead an outdoor life.

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